1213-2

THE AMERICAN REVIEW OF TUBERCULOSIS

JOURNAL OF
THE NATIONAL TUBERCULOSIS ASSOCIATION

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VOLUME XXXIV
JULY-DECEMBER, 1936

PUBLISHED MONTHLY
AT MT. ROYAL AND GUILFORD AVENUES, BALTIMORE, MD.
BY THE NATIONAL TUBERCULOSIS ASSOCIATION

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THE VICISSITUDES OF AUSCULTATION

The Address of the President[1]

JAMES J. WARING

In medical practice, inspection, palpation, percussion and auscultation, supplemented by the pulse and respiration counts, thermometry and blood-pressure measurement, comprise the technique of physical diagnosis; from them the physician draws important information and inferences as to the healthy or the unhealthy nature of the person under examination. All of these procedures now enjoy thoroughly respectable positions in the training of the medical student and in the practice of the physician. But it was not always so! Each had to make its own way in the scientific world. In youth all were sadly neglected but the vicissitudes of auscultation will appeal particularly to the sympathies of this audience.

Sired by a man, R. T. H. Laennec, whom we still delight to honor, auscultation was born in the early part of the nineteenth century in the very humble surroundings of a ward in a charity hospital in the great city of Paris. In an incredibly short period of time this little French physician, consumed by the sacred flame of genius and the fever of tuberculous disease, gave to the medical profession an instrument for the examination of the chest and a precise description of what could be heard with it when the lungs were diseased. To-day, a discovery of manifest scientific importance is seized upon almost overnight and subjected, before the month is up, to a thousand trials; a hundred years ago it was different. When Laennec read his "Memoir on Auscultation" before the French Academy of Sciences on the evening of February 28, 1818, it was received, we are told, "with respect but without the slightest trace of enthusiasm." Except by a few of the discerning, auscultation was scorned, even ridiculed. At the time of Laennec's death in 1826, seven years after his book was first published, practically every stethoscope in existence was the product of his own hand. No more significant commentary on the lack of interest of Laennec's medical contemporaries can be imagined!

[1] Delivered at the 32nd annual meeting of the National Tuberculosis Association, New Orleans, Louisiana, April 22, 1936.

Sir Humphrey Rolleston says the appeal of auscultation and percussion was chiefly to the young minds like John Forbes (1787–1861), translator of Laennec's book, James Jackson, Jr. (1810–1834), who first described (1833) prolongation of the expiratory phase of respiration as an early sign of tubercle, Thomas Hodgkin (1798–1866), and William Stokes (1804–1878) who gave us finger to finger percussion. Rolleston might have included the names of William Wood Gerhard (1809–1872) and Samuel George Morton (1799–1851) who was, so far as we know, the only American to study with Laennec. It was Morton who first brought back Laennec's method of auscultation for the benefit of his fellow countrymen in America. Gerhard, called by Garrison the most brilliant American pupil of Louis, was author of the most authoritative work on diseases of the chest before Austin Flint. Sir Henry Halford (1766–1844), President of the College of Physicians of London (1820–1844) and attending physician to George IV, William IV and Queen Victoria, was never converted to the use of the stethoscope. Sir Thomas Watson (1792–1882), one of the great clinicians and teachers of his time, in his "Classical Lectures" (5th Ed., 1871, Vol. 2, p. 20) says the use of the stethoscope for auscultation is, with certain exceptions such as a dirty or infectious patient, "rather a hindrance than a help." In his well known text-book, "The Principles and Practice of Physic," Watson wrote: "I cannot do without the instrument but I do without it as much as I can." In some quarters its use was discouraged as inconsistent with the dignity of a physician.

Imagine a hospital scene of one hundred years ago! At one end of this instrument, the cylindrical wooden stethoscope of Laennec, the squirming perspiring patient pinned to the bed, profanely protesting as the stethoscope, under pressure of the inquiring ear of the physician forcefully plastered against the other end, slides over the poorly upholstered lattice-work of his ribs. Doubtless fastidious medical noses and tender medical ears rebelled.

The flexible, self-adjusting binaural stethoscope, invented by Cammann of New York in 1854, not only spared the ribs of the sick but saved the ears of the stethoscopist from inevitable bruises and gave his nose the welcome protection of six inches further separation from the object of his professional attentions. Contemporary enthusiasm for the new is so great and the advantages of Cammann's stethoscope to doctor and patient so obvious, that it seems strange to read Austin Flint's statement that thirty years after its invention it was not yet in

common use by the profession. In 1925 in his "Reminiscences of Student Life in Europe [during the years] 1879–1881," Dr. Vincent Y. Bowditch, President of this Association in 1908–1909, made the following observations:

> During the progress of the bedside clinics with Wagner and Strümpell, it was interesting to note the attention paid to my binaural stethoscope. Even to the present day the monaural stethoscope is chiefly used in Europe. Not infrequently I was asked to let some assistant or student try my Cammann stethoscope, but as a rule there seemed to be no desire to follow up its use, one of Wagner's assistants remarking to me, "I hear too much. After all it is custom that makes one like his own way best!"

Dr. C. J. B. Williams (1805–1889) of London, who enjoyed probably the largest private practice in diseases of the chest of his time, in his "Memoirs" tells an amusing story of a consultation which illustrates the reluctance of the old physician to try new things. When the attending physician in the case was asked by Dr. Williams if he had examined the patient with a stethoscope,

> The reply was in the negative, with as much contempt of manner as politeness would allow. The senior consultant in this case died soon after, utterly incredulous of the value of auscultation. The junior, one of the most fashionable physicians of this century, wiser in his generation, became a believer when belief in it came into fashion.

Writing in 1882, Austin Flint said that auscultation and percussion were then considered a specialty and that, except in some parts of America, many practitioners made but little use of them.

Dr. R. A. Young, in a recent paper (1930) on "The Stethoscope: Past and Present," relates that the stethoscope came to be more generally employed in England than in the land of its origin. For a long time the French used it only for the examination of the heart and trusted to immediate auscultation for the lungs.

In discussing Young's paper, Sir St. Clair Thompson said that he had seldom seen a stethoscope used in French hospitals and that he had discovered in North America a sanatorium for tuberculous patients where the stethoscope was not only neglected but actually superseded as unnecessary, since it was claimed that the roentgenological examination was more exact. He related an amusing story of a rival of his early days who created a great impression on the public by making his

rounds in a brougham with his hand always on the outside handle, ready to open the door, and in the hand a stethoscope. No wonder, says Thompson somewhat plaintively, that he secured all the patients. Lest a country-wide blossoming of stethoscopes on automobile doors next week embarrass the speaker, I hasten to add that I am making no subtle suggestions for the improvement of business. To-day even the surgeons own stethoscopes and appear to be able to use them, although I am occasionally reminded of Professor Trousseau's story of the deaf French physician, *Il ausculte toujours*, said Trousseau, *il entend jamais* [He always listens but never hears anything].

Years ago Lawrason Brown said that the specialist could be distinguished from the general practitioner by the fact that the specialist when he examined the lungs made the patient cough, the general practitioner did not! For the past quarter-century the graduates of every first-class medical school in the United States have been taught the importance of this manoeuvre. To-day, the true expert is distinguished, first, by an abiding faith in inspection, palpation, percussion and auscultation and, second, by a strong conviction that the roentgenogram is best interpreted in the light of clinical impressions. The pseudoexpert is recognized, on the one hand, by his contempt for the stethoscope, a contempt which varies directly with his ineptitude in its use and, on the other hand, by a childlike faith in his own clinical deductions from the roentgenogram.

With the passage of time the stethoscope evolved into a very practical instrument and a score or more of physicians up and down the Atlantic seaboard acquired, by means of it, very fine reputations for their diagnostic skill. A day came when numberless tired feet wore paths to the doors of these experts with the stethoscope. Some of the paths led to great cities like New York, Philadelphia and Boston: others to sparsely settled communities in the mountains far from railroads. Hope and unquestioning faith in the man with the stethoscope, the man with the only instrument that could unlock the morbid secrets of the chest, drew a steadily increasing number of the sick away from their homes to sanatoria located in remote places known as health-resorts. Eventually, when it became recognized that the environment of these institutions and the sanatorium regimen played important parts in the cure, faith in the man and his instrument became submerged in faith in climate, and the reputation of the resort almost eclipsed the reputation of the man. This is not hard to understand. At first the great authorities on the diseases of the chest were few, but as each came to rest from his

labors a dozen younger men, long apprenticed in the craft of auscultation, stood ready to fill his place. Multiplication of the masters of auscultation resulted in the dilution of prestige. There simply wasn't enough prestige to go round. The secrets of the craft became common knowledge. Steadily increasing numbers of young men graduated from the medical schools, well grounded in the fundamentals of physical diagnosis and eager for clinical application of this knowledge. With the decline in prestige of the man with the stethoscope came at length a loss of faith in climate. It was not a deterioration of the elect of the craft that wrought this change. The elect, like the poor, are always with us and they are still good; indeed, they have to be good; but they have made the mistake of multiplying too rapidly. Furthermore, the difference in ability between the expert and his less experienced colleague has been reduced by improvement in the general mass of the profession.

Changing fashions in treatment also have played a part in this revolution in the affairs of the craft of auscultation. Enthusiasm for surgical collapse has on occasion elbowed the man with the stethoscope away from his position of leadership at the bedside and replaced him with a surgeon. Treatment has become social, surgical, institutional, governmental, and no longer remains predominantly personal, climatic and medical.

But roentgenology delivered the most serious blow to the prestige of the specialist on diseases of the chest. Roentgenology not only laid bare the limitations of the stethoscope but exacted unconscious public admission of those limitations. Public confidence in the stethoscope took a bad tumble the moment a patient was referred to the roentgenologist.[2] How could it have been otherwise? It was a confession of inadequacy or futility of the instrument, if not weakness in the man.

"The supremacy of the stethoscope as the means of detecting thoracic disease," says an editorial writer in the British Medical Journal last May, "has been in some danger of being undermined by the applications of diagnostic roentgenology. Probably many practitioners, if given the choice of going over the chest with the stethoscope and looking at a roentgenogram, would at once plump for the film."

This little incident from real life has its significant as well as its amusing points. One fine day in June two well known doctors met by chance on the streets of Saranac Lake. Under the arm of one was the familiar brown manila envelope of large size and known of all men to contain

[2] In a delightful, but I believe as yet unpublished paper on *The Historical Importance of the Removal of the Shirt*, Dr. William Dock of California amusingly dwells on this point.

X-ray films. Ensued this bit of whimsy: First Doctor, with a knowing smile, "What have you there under the arm?" Second Doctor, "X-ray films! I now carry them instead of a stethoscope!"

I have said that other methods of physical examination—inspection, percussion and auscultation especially—made their way slowly. Even roentgenology made its way slowly, but for a different reason. It was nearly two decades after the discovery of roentgenology before the technique of making pictures of the chest had arrived at a point where the physician could place much reliance upon its revelations.

Since the early technical limitations of roentgenology were great, whatever assistance it rendered at first was chiefly in the diagnosis of relatively gross abnormalities such as pneumothorax, pleural effusion, central consolidations and cavity-formation. Recognition of the childhood type of tuberculosis and the earliest evidences of reinfection tuberculosis were the fruits of improved apparatus and technique.

In recent years, in the diagnosis and treatment of tuberculosis, attention has been too much withdrawn from the soil and the seed, and placed, not on the substance of the effect of the seed on the soil, which is the clinical condition of the patient, but on the shadow of that effect. Baldwin aptly says: "We must treat symptoms, not X-ray pictures!" "What is spoken of as a clinical picture is not just a photograph of a man sick in bed," said Francis W. Peabody, "it is an impressionistic painting of the patient surrounded by his home, his work, his relatives, his joys, sorrows, hopes and fears." The roentgenogram is a study of only one of the manifestations of disease. It takes little account of constitution and character which mould or shape for better or for worse the diseases from which a man suffers.

Of course, it is a matter of some local concern that the confidence of the layman has shifted in a measure from the experienced physician with his stethoscope in the health-resort to the roentgenologist, the internist and his surgical colleague in the city. But it is of far greater moment that roentgenography has greatly increased the diagnostic skill of every man who makes intelligent use of it, and, in conjunction with the tuberculin test, is proving a powerful ally in the campaign led by this Association for the nation-wide eradication of tuberculosis. Roentgenography splendidly supplements auscultation. The X-ray is strong where the stethoscope is weak, namely, in the detection of *silent tuberculosis*, by which I mean first infection and minimal tuberculosis of the reinfection type. The masters of auscultation have accurately appraised

and acknowledged its value, but deplore the injudicious enthusiasm of certain of its devotees, which in effect junks the stethoscope, jettisons bedside experience, and puts diagnosis, at the worst in the hands of medically uninstructed female assistants of a roentgenological colleague, at best in the hands of a man who has never seen the patient.

To speak at length in praise of the X-ray would be a terrible bore, to summarize its disadvantages would be no less painful, but on the costliness of roentgenography of the chest I would dwell for a few moments, since the present high cost of radiological diagnosis greatly limits its use. In 1935 the slogan of the Early Diagnosis Campaign of this Association was "Fight Tuberculosis with Modern Weapons." This year that very effective slogan is being used again. To whom is it addressed and what are these modern weapons? Obviously, the X-ray is the most important modern weapon, and the slogan is fired at parents and doctors, all doctors, especially family physicians, not just the experts! It is the ability of the mass of the profession with which we are most concerned.

Unfortunately, not many doctors can install X-ray machines in their offices. Those who can afford to do so are compelled to pass on the heavy maintenance charges to their patients by the collection of fees beyond the ability of many to pay. The benefits of roentgenography of the chest are therefore available only to a small portion of the population. If the apparatus were less bulky the cost of maintenance would be less. If reduction in the cost would place first-class apparatus in the hands of all good internists in this country, it would automatically greatly increase the diagnostic skill of these doctors and ensure the earlier recognition of innumerable cases of tuberculosis of the lungs. I make this statement in full appreciation of the fact that accurate interpretation of the roentgenogram demands great experience and is an art in itself, but auscultation also demands great experience. Although relatively few doctors have mastered the art of auscultation, every doctor owns a stethoscope and, thanks to the educational work of this Association and to improved instruction in physical diagnosis in American medical schools, the general level of skill in the use of this invaluable little instrument is vastly greater to-day than fifty or even twenty-five years ago. It would be tragic indeed if the X-ray, which greatly increases the diagnostic ability of the man at the top, should induce neglect of auscultation by the rank and file of the profession, and thus lead to a general depreciation of physical diagnosis. Repeated

careful comparisons of physical signs with the roentgenogram will greatly improve the skill with the stethoscope of most of us and should take a little of the conceit out of the best of us. The X-ray can make or mar a good physical diagnostician. The stethoscope has been placed unreservedly in the hands of the doctor; the burden of responsibility to see that he is competent in its use lies heavily on medical schools and state boards of medical examiners. Reduction in the initial cost of the X-ray and in its maintenance charges and competent training of all medical students in diagnostic roentgenography of the chest will put in the field a well-trained and well-equipped army to do battle in the campaign against tuberculosis.

In 1828 William Stokes (1804–1878), whose "Introduction to the Use of the Stethoscope" published three years previously was the first treatise in English on auscultation, stoutly defended the stethoscope in words which have not lost force with the passage of time.

> The stethoscope is an instrument [he said] not as some represent it, the bagatelle of a day, the brain-born fancy of some speculative enthusiast, the use of which like the universal medicine of animal magnetism, will be soon forgotten, or remembered only to be ridiculed. It is one of those rich and splendid gifts which Science now and then bestows upon her votaries, which, while they extend our views and open to us wide and fruitful fields of inquiry, confer in the meantime the richest benefits and blessings on mankind. This instrument was first introduced by one whose works will ever remain as an example of patient investigation, philosophical research, and brilliant discovery, and its use is now supported by the liberal and enlightened and scientific portion of the medical world.

Three francs put Laennec's wooden, monaural stethoscope in the hands of the doctor. Three dollars puts the modern instrument in the hands of the medical student. Dwell on this instrument a moment more. Its initial cost is trivial, its maintenance and depreciation charges are not worth mentioning, it does not require an extra room at fifty dollars per month rental to house it, and no extra charge is made to the patient if it proves necessary to use it. It is portable, excessively convenient, almost indestructible. Although some doctors neglect it or use it carelessly, it richly rewards the man who uses it painstakingly. No patient is too poor or too disabled to have the benefits of its use. Regardless of age, sex, color, race or religion, the stethoscope is available for everyone within reach of a doctor. It is applicable in the hos-

pital, in the home or on the street corner. It pours its secrets unreservedly into the ears of him who will only listen, and brings great fame to him who learns best to interpret its small voice.

In conclusion: Are centuries of bedside experience assembled by thousands of observers to be tossed to oblivion while we chase the will-o'-the-wisp of the X-ray through the unreal land of lights and shadows? The answer is: No! The history of physical diagnosis teaches us that nothing good is ever lost. Auscultation increased the value of percussion; roentgenography increases the value of both. Let the slogan of the stethoscopist be: ***Listen, look and listen again.***

BCG VACCINATION IN WESTERN EUROPE[1]

G. GREGORY KAYNE[2]

Few medical subjects as delimited as *BCG* can claim so vast a literature within so short a time. No less than 1,600 books, reports, articles, and even regrettable sheets of invective, had already been written by the end of 1933 (1). An excellent critical review, particularly from the historical and bacteriological aspects, was published in English last year (2). I propose, therefore, to confine myself mainly to discussion of recent work at the European centres I have visited during the past eighteen months. I shall also submit evidence indicating a further attenuation of the *BCG* strain in Paris; and finally, I will attempt to work out the essentials on which a rational application of the vaccine should be based.

In April, 1932, a French ministerial circular requested the *préfets*, that is, the chief administrative local public-health officials, to take all steps necessary to make known and to extend *BCG* vaccination. This year the *Comité National de Défense contre la Tuberculose*, which yearly issues a stamp for the benefit of the antituberculosis campaign, has chosen for the design a photograph of Calmette, who is described as the life-saver of infants by means of *BCG*. If the last two circumstances are contrasted with the fact that in man *BCG* is not employed at all in England, one is inevitably led to infer (unless the English authorities are accused of being human monsters for withholding this life-saving measure) that there must exist ignorance or misunderstanding of the method, on the one hand, or unsubstantiated conclusions and unjustified optimism on the other. The main points in the controversy which has raged round *BCG* are probably familiar to all. Three abstract factors have impressed me as being of additional importance in warping an outsider's judgment. The national character of the *BCG* polemics was clearly demonstrated during the unfortunate disaster of Lübeck, and is probably responsible for the almost reflex accusation of English conservatism as an explanation for the withholding of the vaccine here. Then, too, an antagonistic prejudice must often be born from the strong flavor of advertising in the literature and elsewhere. The mounting figures of

[1] Read before the Tuberculosis Association, February 15, 1935.

[2] London, England. Dorothy Temple Cross Research Fellow in Tuberculosis, 1933–1935.

vaccinated children are shown with an air of finality, based on the false assumption that because an object sells well it must be good. *BCG* has suffered scientifically from bad publicity because it has been *too* well advertised, and there is a tendency to overlook the fact that exaggerated claims may hide a much smaller but nevertheless real benefit. And, lastly, the enthusiasm of some partisans must be measured in relation to the tuberculosis problem in their country. Where the tuberculosis mortality is high, the economic conditions poor, and dispensaries and sanatoria inadequate (as in Spain, for instance), *BCG* clearly appears to offer a simple method of prevention *faute de mieux*.

The difficulty of approaching the subject with an unbiased mind must be considered the first stumbling block to a just appreciation of the effects of *BCG* vaccination.

VIRULENCE OF *BCG*

The question of virulence must take precedence in any discussion of *BCG*. While Calmette's original belief in *BCG* as a *virus fixe* may be considered a hasty conclusion, only the fact of his having been more than a prophet in his own country will account for the persistent rigid attitude of opposition to all evidence brought forward indicating increase of virulence *in vitro* or in animals. Recent work with the tubercle bacillus, and particularly that with *BCG*, has shown the difficulty of fixing a clear line of demarcation between virulence and avirulence. It will assist in understanding what follows if the effects of living tubercle bacilli, in standard doses and standard animals, are broadly classified into three increasingly milder groups: (1) progressive tuberculous disease; (2) tuberculous lesions spontaneously regressive; and (3) lesions not typically tuberculous, but which nevertheless produce some tuberculin hypersensitiveness and immunity. It must of course be clearly understood that all degrees of virulence exist between these broadly defined groups. Bacilli in the first group may be termed "virulent," those in the second "of diminished virulence": both produce lesions reinoculable in animals. *BCG* is claimed to represent the third group—an "attenuated" strain; and the possibility of lesions unassociated with tuberculin hypersensitiveness and immunity must not be forgotten in the application of the vaccine in man. Three questions therefore demand answer: (1) Does *BCG* really never cause progressive or even spontaneously regressive tuberculous lesions in animals or man? (2) Can *BCG*, however grown, increase in virulence so as to produce progressive tuberculosis? (3) Does

BCG, when grown as recommended by Calmette, remain absolutely unchanged, that is, neither increase in virulence nor become more attenuated?

(*1*)

Several authors have reported progressive tuberculosis occurring in a varying percentage of animals inoculated with *BCG:* some of the results, at any rate, have to be discarded owing to probable errors of technique or interpretation. Very many more workers, on the other hand, have only found lesions which, even if histologically tuberculous, were spontaneously regressive. Calmette himself admitted (3) that *BCG* in very large doses may lead to tubercle-formation, but not to caseation, and that these lesions always disappeared and were never reinoculable. It should be added, moreover, especially in view of what will follow, that the positive results (that is, progressive tuberculosis) were obtained in the early years of *BCG* cultivation. In none of the laboratories I visited in seven European countries were positive findings reported to me. Repeated researches at the State Serum Institute in Copenhagen have shown that in guinea pigs all traces of lesions have invariably disappeared after a few months (4).*[3] Domingo in Barcelona has inoculated large numbers of rabbits intravenously with *BCG* (5) and, by sectioning and culturing the organs of animals killed daily, has found that bacilli cannot be demonstrated after 90 days and that no lesions whatever are to be discovered after 200 days. Similar results were obtainable by intraperitoneal injection (6), and in both series of experiments the cellular and histological changes found were not unlike those produced by killed virulent bacilli (7).*

In man definite proof of ill-effects of *BCG* is much more difficult to obtain. Irvine concludes thus (2):

> If we review the whole of this chapter we see a great tragedy in Germany due to a contaminated vaccine, a suspicious but inadequately investigated minor diasaster in Hungary, a doubtful incident in Chile, and several suggestive but quite unproved individual cases. When we consider that 1,343,000 infants have been given the vaccine and there is not yet one sure case of death from the *BCG*, we would indeed be cautious if we still doubted the safety of the vaccine for the normal infant. Even if every case mentioned in this chapter had been proved to be due to the *BCG*, the ratio to the total number inoculated would only have been just under one in 15,000.

[3] An asterisk (*) following a name or statement indicates a personal communication to the writer.

In support of the safety of *BCG* particular emphasis must be laid on Wallgren's series (8). Of 123 infants vaccinated since 1927 and who have not been in known contact with tuberculous contagion, *all* have been followed up and, with the exception of three deaths, have remained in good health until now. The three who died were all examined post-mortem, and the findings (congenital *morbus cordis* with bronchopneumonia, whooping-cough and pneumonia, influenzal pneumonia) could not possibly have been due to the vaccine. Of 230 infants, also all followed up, who have been exposed to tuberculosis, only two have died. While relatively small, I consider this group invaluable because of the exceptional completeness with which it has been studied.

(*2*)

Irvine concludes (2) that it is impossible to ignore and dismiss as experimental errors the results of Petroff, Dreyer and Vollum, and Sasano and Medlar, who stated that, by subculturing *BCG* in certain ways, they succeeded in obtaining a return in virulence. But he points out that numerous workers have failed to confirm the findings of these authors, and that the latter were themselves unable to repeat their results later. In any case, however, the possibility of restoring to *BCG* its virulence by laboratory methods is no contraindication to the application of the vaccination in man provided the routine method of subculture does not have that effect. Indeed, it may be necessary to have at our disposal some method which *will* slightly increase the virulence of *BCG* if it is found to fall to the level where it produces no lesions or lesions unassociated with tuberculin hypersensitiveness and, presumably, immunity. It is therefore essential in order to examine for both slight increases of virulence and any further attenuation to employ a test which will detect small differences in the effect of *BCG*. The procedure of *contrôle* recommended by the Pasteur Institute (9) (10),—that is, the intraperitoneal inoculation of 1 to 10 mgm. of *BCG* in a guinea pig and subsequent examination of the peritoneal lesions,—is too coarse for this purpose (K. A. Jensen[4]). Hence the method being worked out by K. A. Jensen* deserves attention. Healthy guinea pigs are injected intra-

[4] It should be added here that K. A. Jensen, unlike the workers at the Pasteur Institute who assume that a three weeks' growth on Sauton's medium weighs 5 gm., removes the culture from the surface of the medium, drains it on filter paper, carefully weighs it, and then prepares the required dilutions. This is done both for experimental purposes and to obtain emulsions for vaccinating children. This method offers no difficulty in Copenhagen owing to the very small number of children who have up to the present been vaccinated in Denmark.

cutaneously with four dilutions of *BCG* containing 1/10,000, 1/1,000, 1/100 and 1/10 mgm., respectively. Nodules, easily palpable, begin to appear at the site of injections on the second day, reaching their acme about the twelfth, and disappearing generally by the thirtieth day. The number and size of the nodules depend on the strength of the vaccine, *strength* being used here to include alteration in effect due to death of some of the bacilli in the emulsion, as well as to changes in the virulence of the living bacilli.

Calmette and Guérin originally recommended (9) fortnightly subcultures on bile-potato, a passage on glycerine-potato, and two on Sauton's medium preceding the preparation of the vaccinal emulsion. These instructions were soon altered to 10 subcultures on glycerine-potato alternating with two or three passages only on bile-potato (11). This has given rise to some confusion, increased by the omission of mention of the bile-potato passages in the *appendix* on the preparation of the vaccine to Calmette's report on *BCG* at the Conference at Oslo in 1930 (10). And, as a matter of fact, there exists no uniformity in the method of subculture in laboratories at present. Thus, at Copenhagen Sauton's medium only is used (K. A. Jensen*), at Gothenburg bile-potato only (Wassén*), at Stockholm two passages on glycerine-potato alternating with one on bile-potato (Naeslund*) and at Oslo glycerine-potato only, the emulsion being prepared directly from this growth (Voss*).

There is general agreement that there has occurred no increase in the original virulence of *BCG* as grown according to Calmette's last instructions: in fact, the work of animal inoculation and the experiments *in vitro* already quoted tend to suggest that the failure of repeating the positive results may be due to beginning with a less virulent strain. The following work of Jensen is further relevant to this question. In 1927 he obtained a *BCG* strain from the Pasteur Institute which, at first subcultured for a short time on glycerine-potato, was subsequently passed fairly rapidly on bile-potato only. At the end of 1931 he received a new strain from Paris and compared the two by means of the intracutaneous test in guinea pigs. While Jensen's strain gave nodules with 1/1,000 mgm. often and large nodules with 1/100 mgm. always, the Paris strain rarely produced a nodule with 1/1,000 mgm. and smaller ones with 1/100 mgm. This difference could of course be due either to a further attenuation in the glycerine-potato-grown Paris strain or to an increase in virulence in the bile-potato-cultured Jensen strain. That the former alternative is at least partly the explanation is indicated by the fact that a

strain from Paris, obtained in 1933, and the 1931 Paris strain subcultured since by Jensen on Sauton's medium only no longer give intracutaneous nodules with 1/1,000 mgm. and much smaller ones with 1/100 mgm. Moreover, in children he finds that whereas the bile-potato-grown strain produced a large nodule by the intracutaneous injection of 1/1,000 mgm., 1/20 mgm. of the Sauton-grown strain now gives a very small nodule or even no local reaction at all.

While in Paris, I was able to collect clinical evidence indicating further attenuation of the Pasteur Institute strain in recent years.

Dr. Weill-Hallé very kindly gave me full access to the case-records of over 2,000 children followed up in his special clinics at the *École de Puériculture, l'Hôpital des Enfants Malades*, and elsewhere in Paris. The material consists of children vaccinated by mouth since 1924 in various institutions and at home, who are seen in the clinics for the first time at different ages and at greatly varying intervals. They are examined whenever possible with the Pirquet test carried out with Pasteur Institute tuberculin (pure) and by the scarification method, and revaccinated, generally subcutaneously, at one year of age and/or later. A certain number receive their first vaccination subcutaneously at the clinics some time after birth. While I consider the material, method of follow-up, and tuberculin-testing insufficiently uniform or complete for the determination of absolute criteria like mortality, tuberculin sensitivity, etc., I believe, since there have been no changes in the type of material, methods used and staff engaged in the work for many years, that the figures to be quoted are sufficiently accurate for the purpose of comparison during that period. In order to have the data available after leaving Paris, and to enable them to be classified and checked, I studied the case-papers of the whole series and transferred the essential data on an index card I designed for the purpose. The effect of the vaccine was examined in two ways: (1) by comparing the percentage of nodules and abscesses which followed subcutaneous vaccinations and revaccinations year by year, the same dose being used—the latter criterion necessitated taking 1928 as the earliest year; (2) by comparing the percentage of positive Pirquet tests obtained after oral vaccination at birth year by year in three-monthly periods up to the age of 15 months. Contacts, non-contacts and those in which possible contact cannot be excluded were considered separately. I subsequently submitted my figures to Dr. Rasch, statistician to the State Serum Institute in Copenhagen, whose conclusions I shall quote.

Nodules and abscesses followed subcutaneous vaccinations, all the children being grouped together, in roughly 50 per cent in each of the years 1928, 1929 and 1930, but in only about 4 per cent in 1931 and 1932. In table 1 the years 1928–1930 and 1931–1932 were therefore grouped together. The worst possible difference in the two groups (taking into account the few children who were not seen after the injection) is 9.8 times the standard deviation and therefore quite significant.

TABLE 1

Subcutaneous vaccinations and revaccinations

(Dose $\frac{1}{10}$ and $\frac{1}{5}$ mgm. *BCG*)

YEARS	CONTACTS			SUSPECTS			NO CONTACT KNOWN		
	Number vaccinated	Abscesses and nodules		Number vaccinated	Abscesses and nodules		Number vaccinated	Abscesses and nodules	
		number	*per cent*		*number*	*per cent*		*number*	*per cent*
1928–30	42	25	59	27	15 (16)	56 (59)	31	18	58
1931–32	101	2 (5)	2 (5)	67	5 (6)	8 (9)	87	2 (7)	2 (8)

(Numbers in parentheses represent figures assuming that children not seen or heard of since vaccination had developed an abscess or nodule.)

As there are no significant differences between the percentage of sequelae in the three groups they can be grouped together.

YEARS	NUMBER VACCINATED	ABSCESSES AND NODULES		WORST POSSIBLE DIFFERENCE	STANDARD DEVIATION	QUOTIENT
		number	*per cent*			
1928–30	100	58 (59)	58.0 (59.0)	50.9	5.2	*9.8*
1931–32	255	9 (18)	3.5 (7.1)			

The difference between the percentage of sequelae in the years 1928–30 and the years 1931–32 is quite significant—about 10 times the standard deviation.

The argument might be brought forward that this difference is accounted for by a more careful exclusion of tuberculous infection before vaccination by means of tuberculin-testing in the more recent group, as it is assumed that naturally infected children are likely to develop after *BCG* an abscess in the nature of a Koch's phenomenon. I have therefore compiled table 2 to show the percentage of children not tested with tuberculin and tested once and twice respectively before vaccination. It indicates that this factor cannot play an important rôle.

Chart 1 shows the percentage of positive Pirquet tests in the children tested after oral vaccinations at birth at 3 to 5 months, 6 to 8, 9 to 11,

and 12 to 15 months of age. From about 30 per cent to 75 per cent of the children vaccinated were tested, some only once, others at two or more of these periods. In the 12-to-15 months group it was necessary to exclude those revaccinated followed by a positive Pirquet, as it could not be

TABLE 2

Subcutaneous vaccinations and revaccinations

(Dose $\frac{1}{10}$ and $\frac{1}{5}$ mgm. *BCG*)

Preliminary tuberculin testing

YEAR	NUMBER VACCINATED AND REVACCINATED	PER CENT OF LOCAL REACTIONS	NUMBER VACCINATED AT BIRTH	VACCINATED LATER OR REVACCINATED		
				No preliminary Pirquet test	One Pirquet test	Two Pirquet tests
				per cent	*per cent*	*per cent*
1928	26	53	0	0	24	76
1929	130	49	3	10	47	41
1930	37	51	0	10	27	62
1931	55	3	1	9	31	57
1932	200	3	4	2	33	62

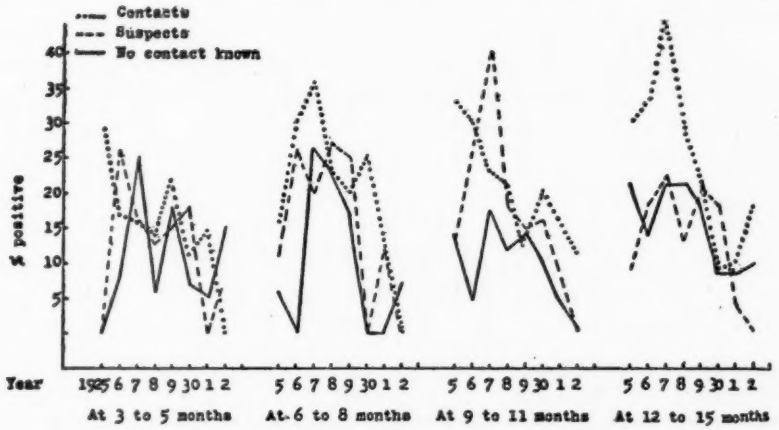

CHART 1. THE PIRQUET TEST IN INFANTS VACCINATED AT BIRTH BY MOUTH
(All positives including feebly positive reactions)

known whether the latter was due to the revaccination or not. In all three groups of children and at all four age-periods there has been a more or less gradual fall in the percentage of positive Pirquet reactions since 1927. Owing to the marked contrast after 1930 in the sequelae of the subcutaneous vaccinations, the oral vaccinations were grouped for 1925–

1930 and 1931–1932. The result is seen in chart 2 and the actual figures in table 3, which also gives the statistically worked out differences. Dr. Rasch concludes thus:

The difference between the activity of the *BCG* before and after 1930 as indicated by the sequelae of subcutaneous vaccinations, is confirmed by the

TABLE 3

The Pirquet test in infants vaccinated at birth by mouth

(All positives including feebly positive reactions)

YEARS	3–5 MONTHS			6–8 MONTHS			9–11 MONTHS			12–15 MONTHS		
	Number tested	Number +	Per cent +	Number tested	Number +	Per cent +	Number tested	Number +	Per cent +	Number tested	Number +	Per cent +
Contacts												
1925–30	134	24	17.9	110	29	26.4	105	24	22.9	171	45	26.3
1931–32	31	4	13.3	41	4	9.8	62	9	14.5	91	10	11.0
Difference			4.6			16.6			8.4			15.3
Diff./St. dev.			0.7			2.6			1.5			*3.3**
Suspects												
1925–30	147	24	16.3	101	20	19.8	107	21	19.6	151	27	17.9
1931–32	34	1	2.9	36	3	8.3	40	3	7.5	56	2	3.6
Difference			13.4			11.5			12.1			14.3
Diff./St. dev.			*3.2**			1.9			2.1			*3.6**
No contact known												
1925–30	171	20	11.7	159	19	12.0	161	21	13.0	186	32	17.2
1931–32	56	5	8.9	57	1	1.8	67	2	3.0	110	9	8.2
Difference			2.8			10.2			10.0			9.0
Diff./St. dev.			0.6			*3.3**			*3.0**			2.4

* Figures in italics are statistically significant.

figures of the oral vaccinations. The differences are all positive and many of them are significant. From the vaccinations by mouth it is, however, not evident that the limit (that is, the year 1930) should be as chosen; the latter has been adopted from the subcutaneous vaccinations. On the other hand, from consideration of the subcutaneous vaccinations it cannot be seen whether only at that time there was an abrupt change in the activity of the *BCG* or whether a steady weakening has taken place.

With regard to the oral vaccinations I must add that we also calculated the figures excluding Pirquet reactions noted as "feebly positive." There was no obvious difference in the conclusions to be drawn.

After learning from K. A. Jensen at Copenhagen of the possible difference in the virulence of *BCG* as the result of cultivation on bile-potato, I was deeply interested to find at Gothenburg that Wassén had continued to grow the strain obtained from Paris in 1926 according to the original instructions, that is, on bile-potato, and that this had served for Wallgren's vaccinations. The next step was therefore to attempt to trace clinically an attenuation or otherwise from Wallgren's material, which he

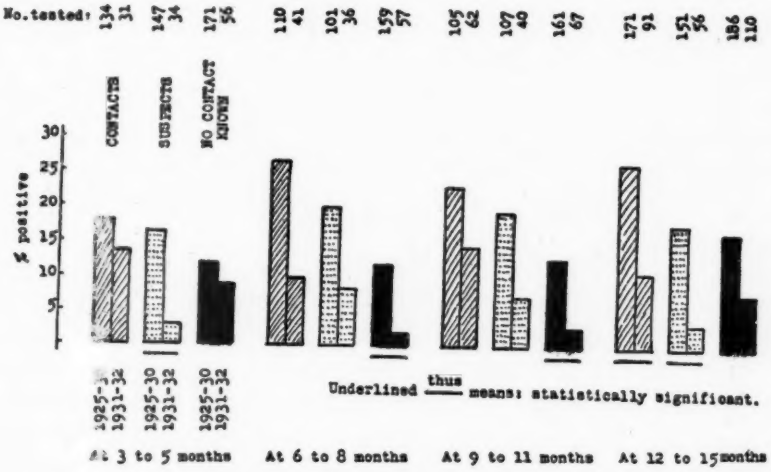

CHART 2. THE PIRQUET TEST IN INFANTS VACCINATED AT BIRTH BY MOUTH
(All positives including feebly positive reactions)

very kindly placed at my disposal. The same method as in the Paris investigation could not be employed here, as Wallgren injects the vaccine intracutaneously, and a successful vaccination always produces a nodule or small abscess. On the other hand, many of the vaccinated children are separated in hospital after the vaccination and examined every week with the Mantoux test till positive. It was possible for me to collect a small series of children who were thus carefully studied and who had been vaccinated with the same dose since 1928. Table 4 shows the percentage of children still remaining Mantoux negative (to 1 mgm., that is, to 0.1 cc. of a 1 in 100 dilution of tuberculin) at weekly intervals. At 7 weeks after vaccination, for instance, 57–70 per cent were still negative in 1929–

32, but only 20 per cent in 1933 and in the first 6 months of 1934. While, owing to the smallness of numbers, it would be rash to conclude that there has been an increase in the virulence of the *BCG*, the figures do not, at any rate, indicate the increasing attenuation found in Paris. I was not

TABLE 4

Percentage of children (Wallgren) still negative to Mantoux test (1 mgm.) after 0.05 mgm. intracutaneous BCG

	1929		1930		1931		1932		1933		1934	
Number vaccinated (Number revaccinated in parentheses)	*27*(4)		*21*(9)		*19*(12)		*15*(3)		*14*(2)		*10*(1)	
Weeks	Still negative		Still negative									
	Number	Per cent	Number	Per cent								
1												
2												
3			21	*100*	19	*100*	15	*100*	14	*100*	10	*100*
4	27	*100*	20	*95*			12	*80*	9	*64*	8	*80*
5	26	*96*	17	*81*	18*	*94*	10	*66*	5	*35*	7	*70*
6	20	*74*	14	*66*	16	*84*			4	*28*		
7	19	*70*	12	*57*	12	*63*	9	*60*	3	*21*	2	*20*
8	14*	*51*			11*	*57*	*				0*	*0*
9	11	*40*	10	*47*	10	*52*						
10	8	*29*	9*	*42*	9*	*47*						
11			6**	*28*	5***	*26*			2	*14*		
12	7	*25*	*		4**	*21*			*			
13	6	*22*	5*	*23*			5	*33*				
14			4*	*19*			*		1	*7*		
15			3*	*14*	3	*15*	4	*26*	0*	*0*		
16	5	*18*	*		1*	*5*	3	*20*				
17	*				0*	*0*						
18			1	*4*			1	*6*				
19	*		0*	*0*			0*	*0*				
20	3	*11*										
.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
26	1	*3*										
27	0*	*0*										

* Week when revaccination became Mantoux-positive.

able to collect any further evidence with regard to this question at Stockholm and Oslo, as in the former *BCG* is little used, and in the latter a vaccine prepared at Oslo itself was employed till 1931 and, for reasons which I shall indicate later, the vaccine from Gothenburg since.

I should like to end this part of my paper with the following provisional

conclusions: *1: BCG* is not a *virus fixe*. *2:* Grown on media like glycerine-potato or Sauton's it very slowly becomes further attenuated. *3:* Grown on bile-potato only it appears not to become attenuated, and perhaps even increases slightly in virulence. *4:* Until recent years, presumably when *BCG* was less attenuated than it is now, its virulence could be increased, when suitably grown, so as to produce progressive tuberculosis in highly susceptible animals. *5:* It is doubtful whether *BCG* even in the earlier years caused progressive tuberculosis when grown according to Calmette's instructions. *6: BCG* is innocuous in man. *7:* The *BCG* used at present appears to vary in virulence in different countries. *8:* For the application of *BCG* in man over a number of years it is essential to find a method of culture which will not attenuate it to the stage when very little or no effect is produced, or, at any rate, some means must be found of slightly raising its virulence when it does so. The last problem is at present engaging the attention of the tuberculosis department of the State Serum Institute at Copenhagen and it is to be hoped that the solution will not be long delayed.

IMMUNITY PRODUCED BY *BCG*

While our chief concern is the extent and duration of the immunity produced by *BCG* in man, results in animals, which alone lend themselves to experimental investigation, owing to the analogy which may be drawn, must be taken into consideration. It would be well, however, at the very outset, to ask what it is we can really expect from *BCG*. Animal experiments have clearly shown the existence of a partial immunity after infection with virulent bacilli. In man, however, two other factors must be taken into consideration. A preëxisting natural immunity may play a rôle in eliminating small doses of bacilli, without tissue changes, both before and after a heavier dose has resulted in a "primary infection." In addition, a constitutional factor may be responsible for the "immunizability" (Lyle Cummins) of an individual, that is, his capacity to develop the necessary defense mechanism in response to invasion by the tubercle bacillus. When this immunizability is high, he will overcome his first infection with a minimal lesion and without developing clinical symptoms. This hypothesis may at least partly account for the great difference in tuberculosis morbidity in the nurses at the Ullevål Hospital in Oslo. Excluding those vaccinated with *BCG*, Heimbeck (14) found that, in 1924–1932, 35 per cent of 266 probationers, Pirquet-negative on admission, developed clinical tuberculous manifestations

subsequently, but only 5 per cent out of 496 Pirquet-positive. The latter, carefully examined before being accepted, represent perhaps a naturally resistant and highly immunizable group, in whom the primary infection was not accompanied by symptoms. This argument is supported by the work of Scheel* among the medical students in Oslo since 1926. He classified the students Pirquet-positive, before commencing hospital work, into two groups: those who had and those who did not have a history of symptoms of tuberculosis. He found the subsequent tuberculosis morbidity to be only 4.3 per cent per observation-year in those Pirquet-negative; 1.4 per cent in those Pirquet-positive without a history of symptoms, but 2.8 per cent in those who had such a history. One cannot therefore accept Heimbeck's* (15) conclusion, on which he bases his *BCG* work, that tuberculin hypersensitiveness is tantamount to almost complete immunity to exogenous infection. The most we can expect from *BCG* is slightly to reinforce the natural immunity and *reduce* the full effect of the first dose of contagion; that is, to turn the scale in some individuals, after which additional immunity will be acquired from the virulent bacilli.

A corollary follows. Great variation is found in the time that both children and nurses become tuberculin-positive after vaccination with the same dose and by the same route, and some remain negative even after repeated vaccination. It is not improbable that immunizability plays a rôle here too, and one might pause to inquire whether the last group in which Heimbeck (14) finds a large tuberculosis morbidity (24 per cent) do not represent a less immunizable, and those who become rapidly tuberculin-positive the more immunizable group, so that the low morbidity in the tuberculin-positive vaccinated nurses is not entirely due to the vaccine.

From these theoretical considerations I pass on to the discussion of the practical determination of immunity—a matter of the utmost difficulty. Before drawing any conclusions as to the effect of *BCG* it is however clearly essential that the vaccine should have entered the tissues and reacted with them. This implies the existence of three conditions.

1: The number of living bacilli in the emulsion should, as far as possible, be constant: The readiness with which *BCG* tends to die after a certain time, when grown on artificial media, has led Calmette to lay down precise instructions with regard to the preparation of the vaccine (10). The culture on glycerine-potato must not be more than 25 days old when employed to inoculate Sauton's medium. The growth on Sauton's

medium should be used for the preparation of the emulsion when 20 to 25 days old. The actual ampoule of vaccine must be administered within ten days of its preparation. K. A. Jensen,* by extensive cultivation and his intracutaneous guinea-pig methods, has found that there is a definite fall in the strength of the vaccine on the fifth day after preparation and perhaps even earlier. It would appear therefore that with present methods it is advisable for greater safety to administer the emulsion within a day or two of its preparation. This argues strongly against the use of a vaccine prepared at any great distance or in another country. The project of carrying out *BCG* vaccination in Greenland, where tuberculosis is very rife and where there are no facilities for preparing the vaccine on the spot, has led K. A. Jensen* to seek for a method of maintaining the bacilli alive for at least 20 days, the time necessary for the vaccine to reach Greenland. It appears that keeping the bacillary growth in a slightly moist state (that is, removed from the medium and drained on filter paper) in the cold may offer the solution.

The importance of this point will be realized in connection with the following incident, the full details of which I was able to gather at Oslo through the kind courtesy of Dr. Scheel. For vaccinating the nurses, Heimbeck, up to 1930, had used a vaccine prepared in the Stattens Institute in Oslo. The tuberculosis morbidity in all the vaccinated nurses was about 4 per cent up to 1930. On June 11, 1930, he vaccinated 10 nurses none of whom became Pirquet-positive; by April 1931, five had developed some tuberculous manifestation (this number later increased to seven). In January 1931, 12 probationers were vaccinated, again with an Oslo vaccine; by July, four had developed erythema nodosum, while, of 10 vaccinated at the same time with a vaccine from Gothenburg, all remained quite well. In view of these results Dr. Scheel arranged for Norwegian, Gothenburg, and Pasteur Institute vaccines to be inoculated on Hohn's medium. No growth resulted from one Norwegian vaccine, and only one colony from the other, while the two Gothenburg and the French vaccine grew very well.

It thus appears probable that the bacilli in the vaccines of June, 1930, and January, 1931, were not alive. Inquiry at the Stattens Institute elicited the information that in June the culture on glycerine-potato was used when 45 days old instead of 25, as there was insufficient growth for the emulsion, which I gathered (Voss*) was prepared without the intervening two passages on Sauton's medium.

In view of what has just been stated, it is necessary to reconsider the

poor results obtained in the nurses at that period, not only because they do not necessarily indicate, as Irvine (2) suggests, a gradual attenuation of the strain, but because the benefit of *BCG* in the whole group would probably be superior to that indicated in Heimbeck's total figures.

Oft-quoted statistics are those of the vaccinated children in Norbotten, north Sweden, in whom a considerable fall in the general mortality is claimed. I shall refer to these later, but, in view of what has been stated, it is of interest to note that the vaccine used there is sent from Stockholm and that it is administered about fourteen days after preparation (Naeslund*).

On the other hand, Wassén* at Gothenburg has been able to grow his *BCG* emulsion when six months old, although this of course only indicates that *some* of the bacilli are alive. Incidentally, Wassén also finds that the growth of *BCG* varies with the source of the potatoes and the salts used for preparing the Sauton medium.

2: All the bacilli in the vaccine administered should gain entrance to the tissues, so that the effective dose in each case can be known. Subcutaneous, intracutaneous, and intramuscular injections may be grouped together as the parenteral method, for in each this requirement will be fulfilled. Administration by mouth, on the other hand, results in a very variable loss of the vaccine from vomiting, possible adhesion to the pharynx, or inhalation with coughing up, and chiefly in the faeces. While, in the application of vaccination on a large scale, these variations may not prove a great handicap, provided a sufficiently large dose is given to ensure some of the vaccine being absorbed, in most cases, for the purpose of determining the *value* of vaccination, the oral method is to be condemned. The point must be raised, however, as to whether any of the vaccine at all is absorbed through the intestinal mucosa. That this occurs is strongly suggested not only in the case of animals but also in infants, 50 per cent of whom, boarded out in the country away from any obvious tuberculous contact, developed, at any rate before 1931, a definite positive Mantoux test (to 2 mgm. tuberculin) at six months (Debré, Lelong, and Pictet (12)); the authors state that a control group of non-vaccinated infants boarded out similarly were all negative to the same dose of tuberculin (but see below). Moreover, postmortem examinations of infants dying of other causes have often shown the presence of considerable abdominal adenitis (Sayé*). In adults the point is difficult to prove owing to the impossibility of excluding infection with virulent bacilli. This argument applies for example to Scheel's* 32 orally vac-

cinated medical students, of whom 11 (of 20 tested) were Pirquet-positive within four months. French workers have made attempts to prove that the *BCG* after oral administration enters the blood-stream and therefore gains entrance to the whole body. In a recent paper Calmette, *et al.* (18) reported isolation of the *BCG* by blood-cultures in four out of 6 infants and two in chimpanzees. While full details are given of the technique of collection of the blood, none are mentioned of the methods used in identifying the organism. Moreover, repetition of the investigation in children while I was in Paris gave entirely negative results. The fallacy of relying upon such signs as enlarged cervical lymph nodes, blood changes, and chest X-rays to prove permeation of the body with the vaccine have adequately been exposed by K. A. Jensen and Ørskov (16). Calmette (18) indicated the Lübeck disaster as proving only too emphatically that tubercle bacilli can pass *via* the intestinal mucosa into the blood-stream. K. A. Jensen and Ørskov (16) have shown, however, that in guinea pigs the passage of living tubercle bacilli beyond the barrage of the peritoneal lymph nodes depends on their virulence and that attenuated bacilli do not pass through. The real crux of the matter is that the parenteral method (and the intracutaneous in particular) may result in a positive tuberculin test more rapidly. This leads to the third condition to be fulfilled.

3: A positive tuberculin test should be obtained, which, if the child has in the interval not been in contact with tuberculosis, is an indication that the tissues have reacted with the bacilli. Calmette maintained that immunity could be present after vaccination even in the absence of tuberculin hypersensitiveness. It would be idle to discuss this point with regard to oral vaccination, as we have no means of judging whether or how much of the vaccine has even been absorbed. With the parenteral method, however, we do know that the vaccine has gained entrance to the tissues, so that the presence of a positive tuberculin test is here presumably an indication that the tissues have actually *reacted* with the bacilli. Again, we come up against the difficulty of the great variations in the time of the appearance of this positive test, suggesting the presence of some undetermined factor which regulates the interaction of the *BCG* with the tissues. In the present state of our knowledge, however, accurate determination of immunity should be based on tuberculin-positive separated children, although it is to be remembered that they may represent in addition a more *naturally* resistant group.

The nature of the tuberculin test to be employed is of some importance.

I have observed great variations in different centres as regards tuberculin used, method, technique, criteria of positiveness and interpretation. In children, at any rate, the Pirquet test when used alone is not sufficiently sensitive, especially when the "boring method" is employed. The notion that *BCG* produces a weak tuberculin hypersensitiveness tends to result in the labelling of very inadequate reactions as positive Pirquet tests. The work of Heimbeck,* Ekberg, Malmros and Roos (19), and Holm (20), has shown that the difference between the Pirquet and the Mantoux tests, carried out to 1 mgm., is less marked in young adults than in children. In view of Heimbeck's vaccination results in the nurses, it should be pointed out that he carries out a second Pirquet if the first is negative (this increases the percentage of positives), and that in recent years this is associated with a Mantoux of 1 mgm. For accurate work the Mantoux test carried out to 1 mgm. (that is, 0.1 cc. of a 1 in 100 dilution), should always be used. Extensive work at the State Serum Institute in Copenhagen (20) has shown the unreliability of results when stronger concentrations of tuberculin are used. As, moreover, they have worked out a very accurate method of standardization of tuberculin by an intracutaneous test in man and have fixed criteria of positiveness, comparison of results of different workers should now be possible.[5]

Determination of Immunity

Only individuals in whom the conditions I have discussed have been fulfilled can be employed for accurate determination of the immunity produced by *BCG*. Before tackling the problem in regard to man a few preliminary remarks on the findings in animals are not out of place. Experiments on laboratory animals are difficult to interpret owing to the latter's high susceptibility and the apparent individual variations. Most workers, however, report a delay in the development of a fatal issue in the vaccinated animals as compared with the controls. It has been possible to investigate cattle by exposing them to natural infection after vaccination. Satisfactory results have been reported in England, Denmark, Italy and Austria, but not in Canada. Professor Jundell, who has taken part in several investigations with cattle and swine in Denmark and Sweden, tells me that the results are not conclusive, and that, in particular, the main difficulty is the impossibility of separating the newly-born calves who cannot be reared without the colostrum of the mother.

[5] It is assumed that the reader is aware of the existence of the International Standard as regards tuberculin. Tuberculin standardized in this unit only should always be used.

Finally, experiments in apes are contradictory perhaps owing to the fact that in Europe the latter no longer live under natural conditions.

K. A. Jensen* (21) has approached the problem in guinea pigs on the lines of Neumann and Lange's work. In a first series of experiments he infected large numbers of vaccinated animals and controls intratracheally, but more recently he has repeated the work by allowing the animals whose heads only are fixed in the inhalation chamber to breathe a very fine emulsion of tubercle bacilli. The animals are subsequently killed at daily or longer intervals, and the lungs are sectioned and carefully examined for histological changes and tubercle bacilli. In this way he is able to study the tissue reactions to single or, at any rate, very few bacilli, and he has been able to show that, whereas in the controls for the first few days endothelial cells with many rapidly multiplying bacilli are to be seen, in the vaccinated animals from the very first the alveoli are packed with mononuclear cells, inside which only one or two bacilli are seen, and it is not till about 15 days after infection that much tissue reaction occurs in the controls and that multiplication of the organisms begins in the vaccinated, resulting eventually in lesions almost similar to those in the controls,—that is, the protective mechanism is only sufficient to *delay* the effect in this highly susceptible animal infected with very virulent bacilli.

Experimental work being out of the question in man, immunity produced by vaccination in the latter can only be determined by considering the tuberculosis morbidity and mortality in vaccinated subjects. Controls are of course essential in view of the declining tuberculosis mortality, especially in children, in recent years. Exact controls as regards all the factors which are supposed to influence the development of tuberculous disease are, however, very difficult to obtain. Even if the enquiry is confined to home-contacts, numerous factors like illness of a tuberculous relative, intimacy and duration of contact, hygienic environment, prophylactic measures, even the weight of the infant at birth must be taken into account. Even then we do not know the rôle played by factors impossible to determine, such as natural immunity and hereditary predisposition. Some of these difficulties are overcome by considering only large numbers, when however the percentage of children not traced rises alarmingly. Moreover, tuberculous disease is difficult to diagnose in infancy and childhood, and different criteria are admitted by different workers. The tuberculosis mortality is probably even less reliable owing to the infrequency with which postmortem examinations

are performed. Realization of these circumstances has led Calmette and many *BCG* workers to employ the figures of general infantile mortality to show the benefit of *BCG*. This has had the malignant result of enabling even a paraspecific immunity to be claimed for *BCG*. When it is considered that tuberculosis even in home-contacts is responsible for a minor portion only of actual *deaths* and that premature and debilitated infants are as a rule not vaccinated, it requires no profound knowledge of statistics to realize how misleading comparisons of the general mortality may be.

In nearly all statistical investigations published it is impossible to affirm that the conditions I have laid down have been fulfilled. Even if it is assumed that the latter are of less importance in mass comparisons, expert statistical opinion outside France (and even in it, although it is not voiced publicly) is unanimous in condemning the statistical methods employed. I should like briefly to comment upon such enquiries that I have personally come in contact with, stressing the work in those which I believe to be of some value in judging the efficacy of *BCG*.

1: Paris: I have already referred to Weill-Hallé's clinics of *BCG*-vaccinated children. I consider that any statistical work of mortality based on them cannot be accepted as "evidence" for the following reasons: *1:* of 1,984 children at least one year old on January 1, 1934, 720 have been in greater or lesser contact with a tuberculous person living in or visiting the home. As, however, there is no intimate connection between the clinics and the dispensaries, details of the illness of the tuberculous person in the household, of contact and of hygienic environment are inadequate. *2:* Moreover, only 25 per cent of these children were in contact with a tuberculous mother; it is to be remembered that Calmette's figure of 24 per cent mortality applied to children in contact with tuberculous mothers only. *3:* Of 428 children first seen at the clinic before one year old, 27 per cent only were seen before three months of age and one-third not till after six months. According to Labeaume (22), a French author, one-half of the total deaths of infants occurs before three months, and three-quarters in the first six months. *4:* The cause of death is often a matter for conjecture. Thus, of 41 deaths which occurred in the whole group of contacts, 13 are labelled as "meningitis," "meningitis (?)", and "tuberculous meningitis (?)"

2: Barcelona: The considerable migration of the population makes it extremely difficult to trace many of the vaccinated children. The fact that, of 4,200 vaccinated, only 1,486 (35 per cent) could be followed (23) is sufficient in itself to render reliable conclusions impossible.

3: Gothenburg (Sweden): Wallgren must be given the credit of being the first to realize the necessity of a "rationalization" of the method of vaccination before any reliable conclusions as to immunity produced could be formed. He carefully excluded natural tuberculous infection in possible contacts, he vaccinated intracutaneously, and he separated the children until, by regular and reliable testing, they were found to be tuberculin-positive. It was not too difficult to obtain the coöperation of parents, as separation of home-contacts in institutions had already for several years been the policy of the health authorities in Sweden. Since 1928 nearly every contact-child has been vaccinated, nearly all have been separated after the vaccination and many allowed to remain in hospital even several months after becoming tuberculin-positive, so much so that 123 out of 355 were returned home actually after disappearance of the source of contagion. In the absence of controls, therefore, the drop in the infantile tuberculosis mortality, which had been 4.3 per thousand in 1912–1921 and 3.4 to 3.9 in 1922–1927, and was only 1.4 in 1928–1932 (8) cannot be assumed to be due to the *BCG* alone, for Wallgren* himself admits that separation of contacts at Gothenburg was not nearly as effectively carried out before the *BCG* vaccination which offers an added inducement to the parents. What prophylaxis alone will do in reducing the incidence of tuberculosis in infants is clearly shown by the work of Heynsius van den Berg (24) in Amsterdam. He divided infants in contact in the first three months of their life with severe sputum-positive cases into two groups: those whose parents were known to the dispensary before the birth of the child and were taught prophylactic measures, and those who were not known till some time afterwards: the tuberculosis mortality (0 to 1 year) was 3.8 per cent in the first group and 35.7 per cent in the second.

More may be deduced, however, from the extremely low incidence of tuberculosis in Wallgren's (8) 230 vaccinated children who returned to contact, although only 29 returned before the age of three months: there has been only one case of definite tuberculous infiltration and no deaths from tuberculosis (the two who died having been autopsied). Again I would impress the fact that all the children have been very carefully followed up to this date. As only a small number of Wallgren's children returned to contagion before three months of age comparison is perhaps unjustified, but it is nevertheless of interest to note that Heynsius van den Berg (24) found that, when in contact in the first three months of their life, even with very mild sputum-positive cases and with good prophylaxis, the infantile tuberculosis mortality was 2.2 per cent.

While it is thus impossible to state, and Wallgren himself fully admits it, how much the *BCG* has been directly responsible in the very satisfactory results obtained at Gothenburg, it is clear that the vaccination has provided an excellent measure from an administrative point of view on which to base other methods of prophylaxis which might otherwise have been difficult to enforce.

4: Amsterdam: Only infants who risk contact from some member of the family, living in or visiting the home, are vaccinated. When the tuberculous person is in the home vaccination is only carried out on condition that the mother agrees to enter hospital for the confinement. This ensures satisfactory vaccination, the oral method only being employed, and it enables the infant to be separated from the source of contagion for at least two weeks. In order to be able to enquire into the later effects of the primary vaccination, revaccination at one year is not practised. Heynsius van den Berg, Director of the Central Dispensary, and in charge of the vaccination, avoids the pitfall of using for controls infants whose parents have refused the vaccination and therefore likely to be those less interested in the welfare of their children, by using for comparison figures obtained from a series of infants, home-contacts of parents who attended the dispensary before vaccinations began and whose conditions of contact and hygienic environment match, as closely as possible, those of vaccinated children. By choosing the controls in this way, the fall of tuberculosis mortality in recent years is not likely to influence the comparison. Unfortunately, this method enabled only 100 controls to be found. The results obtained by him in 178 children up to date are shown in table 5.* It will be noted that as regards the tuberculosis mortality there is a definite difference in favor of the vaccinated at 0 to 1 year (8.0 per cent and 2.2 per cent), but it is only twice the standard deviation and therefore not significant. On the other hand, the difference at 0 to 2 years (18.0 per cent and 2.7 per cent) is more than three times the standard deviation and therefore statistically significant. Unfortunately, the two groups are not absolutely comparable, as most of the vaccinated infants were separated in hospital for two weeks and this may perhaps influence the results to some extent.

5: Norbotten (Sweden): The vaccinations in this district where tuberculosis is very common are much quoted. Nearly 8,000 children have been vaccinated by mouth. The general mortality is compared with that of over 20,000 nonvaccinated. The infantile mortality is calculated from the 5th day, and found to be nearly half that in the nonvaccinated group. Examination of the first report (23) clearly shows that the weaker infants are not vaccinated, for while "congenital debility" accounts for 30 per cent of the deaths in the nonvaccinated, it is put down as a cause of only 10 per cent of the deaths amongst the vaccinated infants. Moreover, Professor Naeslund admitted to me that he felt that part of, it not the whole of, the apparently satisfactory results *might* be accounted for by the prophylactic measures and better attention given both by parents and dispensary nurses to the vaccinated children.

6: Oslo (Norway): Finally, I shall consider Heimbeck's work amongst the nurses of the large municipal Ullevål Hospital. Subcutaneous vaccination

TABLE 5

Results in children, who during the first 3 months were in contact with open cases in their own family. Vaccinated and control-children

(Heynsius Van Den Berg, Amsterdam)

	GOOD PROPHYLAXIS		BAD PROPHYLAXIS		TOTAL	
	Few bacilli	Many bacilli	Few bacilli	Many bacilli		
First year						
Percentage positive Pirquet:						
control-children	25.0 ± 7.7	43.8 ± 12.4	70.0 ± 14.5	100	49.3 ± 5.9	
BCG-children	36.2 ± 7.0	47.7 ± 6.2	69.3 ± 5.6	93.4 ± 4.6	56.0 ± 3.8	
Percentage tuberculosis morbidity:						
control-children	6.8 ± 3.8	15.4 ± 7.1	37.5 ± 12.1	64.3 ± 12.8	22.0 ± 4.1	
BCG-children	0	1.4 ± 1.4	11.1 ± 6.0	20.6 ± 6.9	6.2 ± 1.8	
Percentage tuberculosis mortality:						
control-children	2.3 ± 2.2	3.8 ± 3.8	6.3 ± 6.0	35.7 ± 12.8	8.0 ± 2.7	> 5.8 ± 2.9
BCG-children	0	1.4 ± 1.4	3.7 ± 3.6	5.9 ± 4.0	2.2 ± 1.1	
Percentage tuberculosis lethality:						
control-children	12.5 ± 11.7	14.3 ± 13.2	14.3 ± 13.2	38.4 ± 13.5	22.8 ± 7.1	>18.5 ± 7.4
BCG-children	0	3.2 ± 3.2	5.6 ± 5.4	7.1 ± 4.9	4.3 ± 2.1	
First two years						
Percentage positive Pirquet:						
control-children	31.2 ± 8.2	73.8 ± 10.1	83.4 ± 10.8	100	62.4 ± 5.5	
BCG-children	53.9 ± 8.0	70.8 ± 6.6	76.2 ± 9.3	100	72.1 ± 3.9	
Percentage tuberculosis morbidity:						
control-children	11.4 ± 4.2	19.2 ± 7.7	43.7 ± 12.4	71.5 ± 12.1	27.0 ± 4.4	
BCG-children	0	3.6 ± 2.5	13.6 ± 7.3	24.1 ± 7.9	8.2 ± 2.3	
Percentage tuberculosis mortality:						
control-children	2.3 ± 2.2	11.5 ± 6.3	31.2 ± 11.6	64.3 ± 12.8	18.0 ± 3.8	>15.3 ± 4.0
BCG-children	0	1.8 ± 1.8	4.5 ± 4.4	6.9 ± 4.7	2.7 ± 1.3	
Percentage tuberculosis lethality:						
control-children	10.0 ± 9.5	21.4 ± 11.0	50.0 ± 15.8	64.3 ± 12.8	37.5 ± 7.0	>33.3 ± 7.3
BCG-children	0	2.9 ± 2.9	6.2 ± 6.1	8.0 ± 5.4	4.2 ± 2.0	

was commenced there in 1927, when it was found that no less than 35 per cent of the probationers Pirquet-negative on beginning their training (about half the total) developed some clinical tuberculous manifestation in hospital subsequently. The results obtained up to date are summarized in table 6.* Of

TABLE 6

Nurses at Ullevål Hospital

(J. Heimbeck, Oslo)

YEAR	NUMBER OF NURSES ADMITTED	PIRQUET POSITIVE ON ADMISSION					PIRQUET NEGATIVE ON ADMISSION					VACCINATED WITH *BCG*				
		Number	Per cent	Tuberculous disease		Number died	Number	Per cent	Tuberculous disease		Number died	Number	Per cent	Tuberculous disease		Number died
				Number	Per cent				Number	Per cent				Number	Per cent	
1924	109	58	*53*	1	*2*	0	51	*47*	18	*35*	5					
1925	114	42	*37*	1	*2*	0	72	*63*	23	*32*	1					
1926	114	52	*46*	1	*2*	0	62	*54*	18	*29*	0					
1927	121	64	*53*	4	*6*	0	12	*10*	6	*50*	0	45	*37*	2	*4*	0
1928	124	65	*52*	8	*12*	0	19	*15*	11	*58*	0	40	*33*	4	*10*	1
1929	117	61	*52*	3	*5*	0	4	*3*	0	*0*	0	52	*45*	3	*6*	0
1930	108	58	*54*	4	*7*	0	7	*6*	4	*57*	2	43	*40*	12	*28*	1
1931	107	54	*50*	2	*4*	0	26	*24*	9	*34*	1	27	*26*	5	*19*	1
1932	108	42	*39*	0	*0*	0	13	*12*	5	*38*	0	53	*49*	1	*2*	0
1933	107	47	*44*	0	*0*	0	8	*7*	2	*25*	0	52	*49*	3	*6*	0
1934	107	45	*42*	0		0	6	*6*	1		0	56	*52*	0		0
1924 to 1926	337	152	*46*	3	*2*	0	185	*54*	59	*32*	6					
1927 to 1934	899	436	*48*	21	*5*	0	95	*11*	38	*40*	3	368	*41*	30	*8*	3
												P+ 210	*67*	3	*1*	
												312				
												P− 102	*33*	24	*24*	

Those followed up only.

368 nurses vaccinated, 210 are stated to have become tuberculin-positive afterward, and of these only 1.5 per cent developed clinical tuberculosis, 102 did not become tuberculin-positive and, of them, 24 per cent developed tuberculosis. The remaining 56 left and could not be followed up. Grouped together, this

gives a tuberculosis morbidity of 8 per cent, as compared with 40 per cent in 95 nurses who refused to be vaccinated and 5 per cent in those tuberculin-positive on entrance. This interesting work of Heimbeck, which is considered by many as possessing the characters of a perfectly controlled human experiment, requires critical examination. In the first place, I would draw attention to the theoretical considerations put foward earlier with regard to the rôle of immunizability. In addition, certain details in the investigation indicate that there has been considerably less accuracy than is supposed, for the following reasons: *1:* The unreliability of the Oslo vaccine used till 1931. Doctor Heimbeck very kindly let me have certain details with regard to the sequelae of the vaccinated, which are collected in table 7. The difference in the virulence of the Oslo and Gothenburg vaccines used since 1931, as judged by subsequent

TABLE 7

Vaccinated nurses at Ullevål Hospital

(J. Heimbeck, Oslo)

YEAR	NUMBER VACCINATED	P+ (INFILTRATION 2 MM. OR MORE)	P+ (INFILTRATION LESS THAN 2 MM. IN DIAMETER)	P+ AND LOCAL INFILTRATION	P+ AND LOCAL ABSCESS	P− AND LOCAL INFILTRATION	P− UP TO 6 WEEKS AFTER VACCINATION OR UP TO INFECTION IF OCCURRED BEFORE	NOT TESTED DURING FIRST 6 WEEKS	LEFT BEFORE CLASSIFICATION IN OTHER GROUPS POSSIBLE
1927	45	23	7	8	2		3	1	1
1928	40	9	6	6			13	4	2
1929	52	11	1	5	1	2	4	24	4
1930	43	5			1		36		1
1931	27	1	2	1	11	3	7		2
1932	53		1	16	29	4	3		
1933	52		1	28	15	5			3
1934	54			27	22	4			1

P. = Pirquet test.

tuberculin hypersensitiveness and formation of nodules and abscesses, is very obvious. *2:* The determination of tuberculin hypersensitiveness after vaccination was, however, until recently not carried out uniformly or frequently. Moreover, although the probationers were not placed in the tuberculous sections immediately after vaccination, they were nevertheless working in the general wards, so that some of the positive tuberculin tests may have resulted from a virulent infection. *3:* Quite an appreciable number of the nurses in 1927 and 1928 were deemed Pirquet-positive with a reaction less than 2 mm. in diameter. These three factors appear to me to make Heimbeck's classification of the vaccinated into Pirquet-positive and Pirquet-negative as a result of the vaccination far too uncertain for basing morbidity figures in the two groups. This does not detract, however, from the significance of the relatively low morbidity in the total vaccinated.

I may add that the figures since 1932 are much more significant, as not only is a reliable vaccine being used and the Mantoux test carried out, but, in addition, owing to the establishing of a preliminary school for the nurses, the latter are now under regular observation by Heimbeck for four months before beginning work in the wards.

Duration of Immunity

If it is assumed that *BCG* vaccination produces some immunity, the next point to decide is how long this partial immunity lasts. Unfortunately, there is no criterion by which we can judge this in man. It does seem possible, however, to determine the duration of the tuberculin hypersensitiveness after vaccination. In order to enable this to be done the children must clearly have avoided virulent infection. Debré, Lelong and Pictet (12) concluded, as a result of their work on the children at the *Oeuvre du Placement Familial des Tout-Petits*, where home-contacts are separated by being boarded-out in the country, that tuberculin hypersensitiveness after vaccination lasts at any rate up to the age of five years. Their conclusions are not valid for the following reasons: *1:* The environment in the country cannot be considered as absolutely tuberculosis-free (see report on *Prevention of Tuberculosis in Childhood by Methods of Separation*, by the writer (26)). *2:* The *same* children were not followed up to five years of age. *3:* Their criteria in interpretation of the tuberculin test must have led to the inclusion of reactions not specifically positive (see criticism below). I have, however, been able to obtain more reliable evidence in this connection at Oslo. Dr. Brinchmann,* who is in charge of one of the institutions for the separation of home-contacts from birth to the age of 3 years, has been able to follow up a small number of intracutaneously vaccinated children up to that age, whom he has tested weekly à la Pirquet or Moro and, when negative, intracutaneously with 1 mgm. In this way he found in one series of 15 children that, after a first successful vaccination, the tuberculin hypersensitiveness lasted under six months in five and from six to twelve months in five more; in two it lasted over two years. In another series of twenty, still in the home, the tuberculin test in seven became negative at six months or less, and in two at the age of two years. Revaccination in children, who became tuberculin-negative again after vaccination, results in a much shorter duration of hypersensitiveness.

To summarize: Scientifically accurate determination of the effect of *BCG* in man is impossible, because it is an effect which cannot but be

small. *A priori* evidence (lesions and tuberculin hypersensitiveness following vaccination, and K. A. Jensen's inhalation experiments on guinea pigs) and two or three statistical investigations containing less of the gross errors indicate that (1) *BCG* vaccination produces a very partial immunity, which is only likely to play an effective rôle when it is combined with other methods of prophylaxis; and (2) the duration of the immunity varies considerably, but is generally between six and twelve months; hence, it is important that a vaccinated child, who must return to tuberculous contact in the home, should do so as soon as it has become tuberculin-positive after the vaccination.

THE RATIONAL BASIS OF *BCG* VACCINATION

We are now in a position to consider the essentials on which to base a rational application of *BCG*.

1: The vaccine must be as far as possible of a standard strength.
2: A method for detecting small differences in the strength of the vaccine is desirable.
3: The preparation of the emulsion and the date it is used should be such as to ensure a more or less constant number of living bacilli at the time of the administration.

These three points have already been discussed.

4: A suitable route of administration must be employed. The importance of parenteral administration in ensuring that the whole of the dose administered gains entrance to the tissues has already been indicated. Intramuscular injection has not been extensively used and will not be further discussed. It appears to offer no advantages over the other methods, and has the definite disadvantage that, should an abscess occur, it is not readily accessible for inspection or aspiration. After both subcutaneous and intracutaneous injections, localized infiltration (the rule in successful intracutaneous vaccinations) follows, resulting with varying frequency in a cold abscess which may resorb, or discharge for weeks or months before finally healing and leaving a scar. The following factors have to be taken into consideration:

A: Abscess-formation is more likely to occur in a naturally infected person (Koch's phenomenon). As abscesses have occurred even after the very careful method for excluding tuberculous infection employed by Wallgren*, (see below), I cannot agree with Sayé*, who believes this to be

the chief cause of an abscess. He attributes the absence of abscesses after his subcutaneous vaccination in recent years (a fact also noted by Duthoit* in Brussels) to the more careful exclusion of virulent tuberculous infection by the use of 1 cgm. of tuberculin for the Mantoux test. His findings may be due to a further attenuation of the *BCG*. In newborn infants no preliminary tuberculin testing is necessary. In infants or children who may have come in contact with tuberculous contagion it is essential in view of the ante-allergic period which is considered by most authorities to be about six weeks. The ideal procedure is to separate the child for that period and test every week with a Mantoux of one mgm. This is the method generally used by Wallgren. I believe, however, that in actual practice, by taking into account the opportunities for contact and other factors, it should be possible considerably to simplify this rigorous procedure and one can often be content with two Mantoux tests at a 2- or 3-week interval, prophylactic measures being taken in the meantime. It is of course important not to vaccinate a naturally infected child, also in order to avoid subsequent tuberculosis being considered as due to or as having occurred in spite of the *BCG*.

B: The dose and virulence of the vaccine are the most important factors in the formation of abscesses. The individual variations in the reaction of children to *BCG* vaccination are not sufficient to invalidate the finding that there is a direct increase in number and size of abscesses following increase in the dose of vaccine administered. That the virulence plays an important rôle is shown not only by the experience of K. A. Jensen*, who a few years ago obtained large abscesses while a much larger dose now gives only a small nodule; but, by comparing the results of the following workers, all using the subcutaneous method.

Miralbell* (Barcelona), for instance, injects 0.25 mgm., and has obtained only one abscess in a series of about 300 newborn infants. Weill-Hallé (Paris) uses 0.02 mgm. in older infants or children, and has in recent years obtained only about 3 per cent of abscesses or nodules in spite of relying for the exclusion of tuberculous infection on one or two Pirquet tests without separation only; yet Kristenson* (Upsala), using the Gothenburg vaccine, obtains abscesses in nearly every child although he uses only 0.04 mgm. distributed in four places. In adults, both Kristenson* and Heimbeck (see table 7) very frequently obtain abscesses in nurses with the Gothenburg vaccine, using 0.04 mgm. (in four places) and 0.10 mgm., respectively.

No one worker appears to have made sufficiently extensive comparison

between subcutaneous and intracutaneous administration, and comparison between the work of different authors may be fallacious owing to the different strengths of the vaccine. However, the intracutaneous method appears to be the better of the two. It has the disadvantage that the technique of administration is a little more difficult and that the nodule or abscess formed later is more prominent. On the other hand, it possesses many advantages. (1) The infiltration or abscess is localized and tends to heal more quickly. (2) Both at Oslo and Gothenburg it has been found that, while a local reaction is not always followed by a positive tuberculin test, the latter never results in the absence of such a local reaction, so that the absence of a nodule at the end of three or four weeks is a good indication for revaccination without any further loss of time. (3) The following theoretical considerations suggest that intracutaneous injection may aid the formation of immunity: the well-known capacity of the skin as an antibody-producer, and the slower absorption which may act on the principle of repeated small doses. Work on guinea pigs at the Pasteur Institute has shown that repeated small doses of *BCG* give a better and quicker immunity to the animals than the total amount given in one dose. Jensen*, acting on the same principle, administers the *BCG* intracutaneously in two doses at an interval of four weeks.

The oral method of vaccination has been much condemned,—a little unjustifiably, perhaps; for it is very simple and does not possess the inconvenience of local sequelae. Review of the literature indicates, however, quite clearly that it does not produce so many positive tuberculin tests afterward, nor so quickly. Moreover, the work on Weill-Hallé's children already discussed has shown that this percentage is still further dropping. Debré, Lelong and Pictet (12) have claimed finding that 97 per cent of children orally vaccinated at birth (and boarded out in the country) subsequently became tuberculin-positive. Their work, however, can be criticized in many respects: (1) The tests were carried out with eight increasingly stronger solutions of tuberculin up to 1 cgm. No controls of broth were used with this last dose, recommended by Hart (17). While 10-mm. erythema and infiltration were apparently considered the minimum for a definite positive reaction with the weaker dilutions, this limit was lowered for the stronger concentrations, although the contrary would be more logical in view of the possible sensitization to the peptone in the broth. (2) Many of their positives were "feeble," that is, indefinite reactions with 1 cgm. tuberculin (1 in 10), or *ébauchées*, —staining appearing at the sites of the first injections after the whole

series has been employed. They justify their inclusion of these reactions as positive by stating that they did not find them in 120 nonvaccinated children. Reference to the work on these controls shows, however, that 85 were examined with a Pirquet test only and 35 with a Mantoux up to 1 mgm. only. Nevertheless, if we accept as the criterion of a positive test a Mantoux up to 2 mgm., their figures give 30 per cent positive at three months and 50 per cent at six months. More recently the same authors (13) vaccinated by mouth 130 children ten months to four years old either for the first time or as a revaccination. Only 13 per cent were definitely Mantoux-positive at six months. They suggest that these low figures indicate that the intestinal mucosa is less permeable at this age. In view of what has been stated, I think it is at least probable that the poorer results may also be due to the greater attenuation of the vaccine. In a further note (25), the authors show that, of 140 children of the same ages vaccinated at about the same period with 0.03 mgm. subcutaneously, about 57 per cent were definitely Mantoux-positive six weeks afterward. For comparison it is interesting to note that Wallgren (1929–1931) obtained 30–35 per cent positive at six weeks, but in the last two years the percentage is about 70.

It is clear that the oral method cannot be recommended except for use by workers advocating mass inoculation of all infants at birth, and it has the further disadvantage inherent in its very simplicity that its administration is often delegated to parents or untrained individuals who may not bother to replace a dose vomited or lost in some other way.

5: A dose of vaccine should be used which will produce tuberculin hypersensitiveness as rapidly as possible with the least inconvenience. In oral vaccination the dose (3 cgm. in three doses at one- or two-day intervals) is intended to be big enough to compensate for losses through the causes mentioned above. As far as I know, no work has been carried out to discover whether an even greater dose, given orally, will produce tuberculin hypersensitiveness more often or more quickly. There is the theoretical danger of causing large abdominal lesions.

For intracutaneous work it is essential that the dose should be accurate. At the Pasteur Institute it is assumed that at three weeks the growth on the Sauton's medium weighs exactly 5 gm., but this appears too rough a procedure. Both at Copenhagen and at Gothenburg the growth is drained on filter paper and then weighed. The dose should be the biggest which can be used without causing an abscess. At present it

varies in different countries. In children, subcutaneously, Weill-Hallé uses 0.02 mgm., injected over the lower angle of the scapula; Debré, 0.03 mgm., in 3 doses given simultaneously in the back and thighs; and Miralbell 0.25 mgm. Intracutaneously Wallgren employs 0.05 mgm., injected in the lateral part of the thigh, and K. A. Jensen 0.05 mgm., followed by another 0.05 mgm. in about two weeks' time. The question of fractioned doses deserves further earnest study.

6: The children should not be in contact with tuberculous contagion until a positive tuberculin test after the vaccination is obtained. A great deal has been said about the difficulty of obtaining adequate separation, the dangers of herding together infants in institutions, and so on. I believe that the difficulties associated with this question are to some extent exaggerated. An efficient tuberculosis organization does not treat the tuberculous patient only, but his whole family. Vaccination of a contact-child will therefore take place parallel with the treatment of the patient, institution of prophylactic measures in the home, and assistance to the family. This means that in a large proportion of cases, with a certain amount of care, the infant or child may be allowed to remain at home. When the infant must be removed from home for some weeks, it should be admitted, not to a hospital or an institution caring for or having a staff dealing with sick children, but in a home reserved solely for healthy infants. Norway and Sweden have had extensive experience in the institutional separation of home-contacts. While the accurate computation of mortality statistics is difficult for many reasons, nevertheless one cannot but be impressed by the absence of deaths due to intercurrent as compared with a hospital group. Finally, I consider that tuberculin-positive and -negative children should be kept apart in these institutions and that, whenever possible, human milk should be used for feeding.

7: Only children definitely risking contact with tuberculosis should be vaccinated. Three groups of individuals must be considered, namely, (A) newborn infants, (B) older children, and (C) adolescents.

A: Newborn infants: The controversy is still raging as to whether only contacts or all infants are to be vaccinated. In France and Spain the latter procedure is advocated; in Holland, Denmark, and Norway only contacts are generally vaccinated. In deciding this point the chief consideration is the proportion of infantile tuberculosis directly due to

family contagion. Heynsius van den Berg* points out that in Amsterdam the number of infants dying of tuberculosis not having been in contact in their homes is so small as not to warrant the vaccination (which in any case does not offer a guarantee of protection in every individual) of several thousand children. In Gothenburg this argument applies even more effectively. But, clearly in certain European countries where tuberculosis is rampant and economical conditions very poor, the occasions for chance infection are infinitely greater.

One must, of course, consider the danger from bovine sources, not equally recognized or admitted in different countries, and it might be argued that this is sufficient justification for the general vaccination in countries where there is much bovine tuberculosis and breast-feeding is not the rule. This point is, however, perhaps of greater importance in considering older children.

B: Older children: Although in them the tuberculous mortality is very low, the very crippling morbidity deserves active measures. Vaccination, after careful exclusion of virulent infection in home-contacts, is certainly indicated. Even where bovine tuberculosis is rife there seems little justification for the recommendation of general vaccination, mainly because it would be prevention against an insufficiently known danger, and because the immunity lasts a short time only. Repeated vaccinations by the parenteral route with careful tuberculin-testing wholesale would be quite impracticable.

C: Adolescents: The work of Heimbeck and Scheel among nurses and students has indicated the field for the use of the vaccine in adults. Before any such measure is applied in another country, however, it is essential to know whether the same problem exists in the latter. In England we are hardly in a position to dogmatize as to the tuberculin sensitization of nurses and students beginning hospital work, or as to what may be the subsequent danger they run. Such investigations must therefore precede any consideration of the use of vaccination in them.

SUMMARY AND CONCLUSIONS

To summarize: BCG produces a very partial immunity, which is effective only if the vaccination is combined with other methods of prophylaxis. Certain conditions as regards the vaccine and its administration must be fulfilled. The indication for its use must depend on the amount of tuberculosis and the extent of the antituberculosis organization in each country; but, in most European countries at any rate, it should be confined at present to infants and children in contact with tuberculosis in

their homes. The vaccination of tuberculin-negative adults likely to be in much contact with tuberculous patients must be considered. In organizing *BCG* vaccination in a country it is essential that the vaccine be prepared on the spot, and that each country should itself work out the details of the application according to results obtained, and the aim in view; that is, the scientific determination of immunity produced by *BCG*, or having accepted the latter as a fact, merely the use of the method for prophylaxis. *BCG* does not, I consider, mean reorganization of our present scheme of dealing with tuberculosis; it would best be applied working hand in hand with it.

In concluding, I offer the complexity of the subject and the difficulty of obtaining reliable evidence as some excuse for my shortcomings during the past hour. I have endeavored to show that, in regard to the claims put forward by enthusiasts, we have been justified in emulating the prudent man who looketh well to his going, rather than the simple who believeth every word. Two facts with regard to *BCG* are, nevertheless, now emerging: it is harmless, and it is of some value if used, under certain conditions, as an adjunct to other methods of prophylaxis. Indeed, while paying a tribute to Calmette, who fought against very heavy odds at times to generalize a method which he believed to be a complete solution to the problem of tuberculosis in man, one feels that the cause of *BCG* would have been better and sooner served if he and his followers had remembered the words which the famous Ernest Renan once said to an overenthusiastic Pasteur:

Truth, Sir, is a great coquette; she will not be sought with too much passion, but is often most amenable to indifference. She escapes when apparently caught, but gives herself up if patiently waited for; revealing herself after farewells have been said, but inexorable when loved with too much fervour.

It is a very great pleasure to express my sincere gratitude to the workers mentioned in the text for their unfailing courtesy, their constant readiness to place all information and records at my disposal, and their kindly patience in listening and replying to criticism which must have been very trying at times.

I also wish to express my deep appreciation of the generous facilities given me by the *Medical Research Council* during the tenure of my Fellowship.

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THE EPIDEMIOLOGY OF TUBERCULOSIS IN KINGSTON, JAMAICA[1]

A Study of Infection as Indicated by the Tuberculin Test[2]

C. W. WELLS AND H. H. SMITH

A survey to determine the incidence of tuberculous infection and disease was undertaken in four separate areas in the city of Kingston, Jamaica, beginning in August, 1931, and ending in February, 1934. The areas were selected to represent different social, economic, and racial conditions existing in this particular city.

Areas 1 and 2 were peopled largely by the poor laboring class, with black and dark brown the predominating colors. In area 1, 87.5 per cent and in area 2, 76.9 per cent of the population were so described. In area 3, the population comprised 53.4 per cent black and dark brown, the remainder being largely light brown. About half the population belonged to the lower working class, while the remaining half might be designated as of the middle class. Area 4 comprised 48 per cent black and dark brown, 16.8 per cent white and miscellaneous, and the remainder light and pale brown. In the main, the inhabitants of this area were of the better class.

Considerable difference with respect to the density of population was found in these areas. In areas 1 and 2, the density was approximately 82,000 and 96,000 persons per square mile respectively; while in area 3 there were approximately 20,000 persons per square mile, and in area 4 approximately 9,000 persons per square mile.

The economic conditions in each area were reflected in a measure by the average size of each household; this was found to be:

Area 1	2.794	Area 3	4.005
Area 2	3.054	Area 4	4.949

[1] The studies here reported were conducted with the support and under the auspices of the International Health Division of The Rockefeller Foundation in coöperation with the Jamaica Government Medical Department.

[2] This report is part of a larger and more extensive study of the epidemiology of tuberculosis in Kingston, Jamaica; the more detailed report and tables are published officially by the Jamaica Government.

Thus the average size of the household increased in general with improvement in economic and social conditions. On the other hand, the reverse was noted with respect to the number of persons per room, for in areas 1 and 2 there were found 3.0 persons per room; 2.5 in area 3; and 1.6 in area 4.

An important contribution to the study of the epidemiology of tuberculosis has been an estimate of the distribution of infection in different parts of the world. To obtain such information it is necessary to test adequate numbers of individuals of all ages, selected at random, so as to represent a fair sample of the population studied. This report presents the results of tuberculin tests applied to random samples of the population in a large tropical city. Each area was investigated separately and in as short a space of time as possible.

The tuberculosis literature lacks reference to studies designed to determine the level of tuberculous infection in an unselected or random population. Numerous reports are available, dealing with the findings in highly selected groups and classes of the general population; such as school children, inmates of hospitals and other institutions, dispensary patients, as well as various groups of industrial workers. Such studies are of great value, but whether or not the results obtained reflect the actual prevalence of infection in the general population is an unsettled question. The results herein presented may be considered as adequately showing the amount of infection in groups of the population in which the element of selection plays a negligible rôle.

The Mantoux or intracutaneous tuberculin test was employed throughout this investigation, using O. T., lot no. 341.6, prepared by the Gilliland Laboratories. Fresh solutions were prepared for each day's tests. In the initial test 0.1 cc. of 0.01 mgm. was employed. Forty-eight hours later, negatives to this dose received a second injection of 0.1 cc. of 1.0 mgm. The technique in every respect, as well as the grading of reactions, followed exactly those described by Opie (1).

A reaction expressed by one plus (+) is a definite oedema, not more than 10 mm. in diameter and raised about 1 mm.; the area of redness is less significant and is usually larger.

A reaction of two plus (++) is a well-defined oedema in an area from 10 to 15 mm. across and is raised somewhat more than 1 mm., with redness extending beyond the oedema.

A reaction of three plus (+++) is an extensive oedema, measuring more than 15 mm., but with no necrosis of the skin, and in a few instances redness extending along the course of the lymphatics adjacent to the site of injection.

A reaction of four plus (++++) is extensive oedema, redness and a spot of necrosis; it may be associated with malaise and elevation of temperature.

The results of this study are presented under the following headings:

1: The results of the tuberculin test for each area, by age and sex.
2: The results of the tuberculin test for each area, by age, sex, and color.
3: The intensity of the tuberculin reaction.
4: The results of the tuberculin test in relation to age and length of residence in Kingston.
5: The results of the tuberculin test in relation to history of contact with manifest tuberculosis.
6: The results of the tuberculin test in relation to occupation.
7: The results of the tuberculin test in relation to size of household and the number of individuals per room.

1: The Results of the Tuberculin Test for Each Area, by Age and Sex

Some variation occurred in the proportion of the total population tested in each area, the percentage tested in each area being as follows:

	per cent		*per cent*
Area 1	79.6	Area 3	90.5
Area 2	77.2	Area 4	62.2

Since the same procedures and degree of effort were employed in each area, no ready explanation can be offered for the above differences. It is believed, however, that the number of individuals submitting to the test and the results obtained from it represent a fairly accurate picture of the degree of tuberculization among the population of each area, and permit comparison.

Table 1 gives not only the distribution of the population for each area by age and sex, but also the results of the combined tuberculin tests. The results of these tests for areas 1, 2, and 3 were quite comparable for all ages and total number tested, when the proper correction was made for age distribution. The findings in area 4 for all individuals and both sexes under 20 years of age differed materially from the other areas, the significance of which has been determined, and may be expressed statistically by $X^2 = 30.2$ and $P = 0.0000$. The degree of this

TABLE 1

Population of each survey area, by age and sex, and results of tuberculin test

AGE IN YEARS	SEX	AREA NUMBER ONE					AREA NUMBER TWO					AREA NUMBER THREE					AREA NUMBER FOUR				
		Total Population	Number Tested	Positive to 0.01 mgm.	Positive to 1.0 mgm.	Total Per cent Positive	Total Population	Number Tested	Positive to 0.01 mgm.	Positive to 1.0 mgm.	Total Per cent Positive	Total Population	Number Tested	Positive to 0.01 mgm.	Positive to 1.0 mgm.	Total Per cent Positive	Total Population	Number Tested	Positive to 0.01 mgm.	Positive to 1.0 mgm.	Total Per cent Positive
0–4	M	122	101	26	11	36.6	69	51	9	6	29.4	89	84	22	5	32.1	47	32	2	3	15.6
	F	129	108	22	26	44.4	101	82	18	5	28.0	69	64	16	11	42.2	50	33	8	3	33.3
5–9	M	120	108	39	27	61.1	87	77	31	18	63.6	86	83	38	8	55.4	48	35	11	2	37.1
	F	117	103	45	21	64.1	81	69	22	11	47.8	98	90	37	12	54.4	58	40	4	8	30.0
10–14	M	68	58	34	16	86.2	61	52	32	7	75.0	82	79	43	11	68.4	58	36	18	1	52.8
	F	94	85	54	20	87.1	69	65	37	6	66.2	90	87	52	10	71.3	54	39	18	4	56.4
15–19	M	66	55	37	11	87.3	55	41	34	3	90.2	69	61	45	9	88.5	59	36	21	6	75.0
	F	161	147	113	23	92.5	96	80	47	19	82.5	108	105	71	18	84.8	103	75	47	12	78.7
20–29	M	304	219	185	26	96.3	140	107	89	12	94.4	139	123	108	8	94.3	127	77	67	6	94.8
	F	421	355	278	59	94.9	324	256	203	30	91.0	274	255	206	26	91.0	237	166	134	21	93.4
30–39	M	169	106	95	8	97.2	111	75	67	6	97.3	90	73	70	1	97.3	61	28	27	0	96.4
	F	226	188	159	23	96.8	153	110	87	17	94.5	128	119	104	12	97.5	126	82	68	8	92.7
40–49	M	101	68	62	6	100.0	57	31	23	6	93.5	49	41	37	2	95.1	41	17	17	0	100.0
	F	131	100	85	11	96.0	79	63	51	12	100.0	87	77	68	7	97.4	80	46	45	1	100.0
50–59	M	55	34	32	1	97.1	31	21	18	3	100.0	40	33	32	1	100.0	45	20	19	0	95.0
	F	73	53	34	18	98.1	63	47	41	5	97.9	70	58	47	8	94.8	66	37	36	1	100.0
60 plus	M	30	20	14	6	100.0	23	14	12	2	100.0	30	21	19	1	95.2	27	14	14	0	100.0
	F	52	34	24	9	97.1	40	25	19	3	88.0	63	51	45	5	98.0	66	29	29	0	100.0
Total	M	1,035	769	524	112	82.7	634	469	315	63	80.6	674	598	414	46	76.9	513	295	196	18	72.5
	F	1,404	1,173	814	210	87.3	1,006	797	525	108	79.4	987	906	646	109	83.3	840	547	389	58	81.7
Total		2,439	1,942	1,338	322	85.5	1,640	1,266	840	171	79.9	1,661	1,504	1,060	155	80.8	1,353	842	585	76	78.5
Corrected to standard population						87.5					82.4					83.5					78.7

significance is illustrated in chart 1, where the positive tuberculin percentage by age for each area is diagrammed and fitted with catalytic curves (Muench (2)).

It is obvious that in any sample of the general population a certain proportion has escaped tuberculous infection, and thus will fail to re-

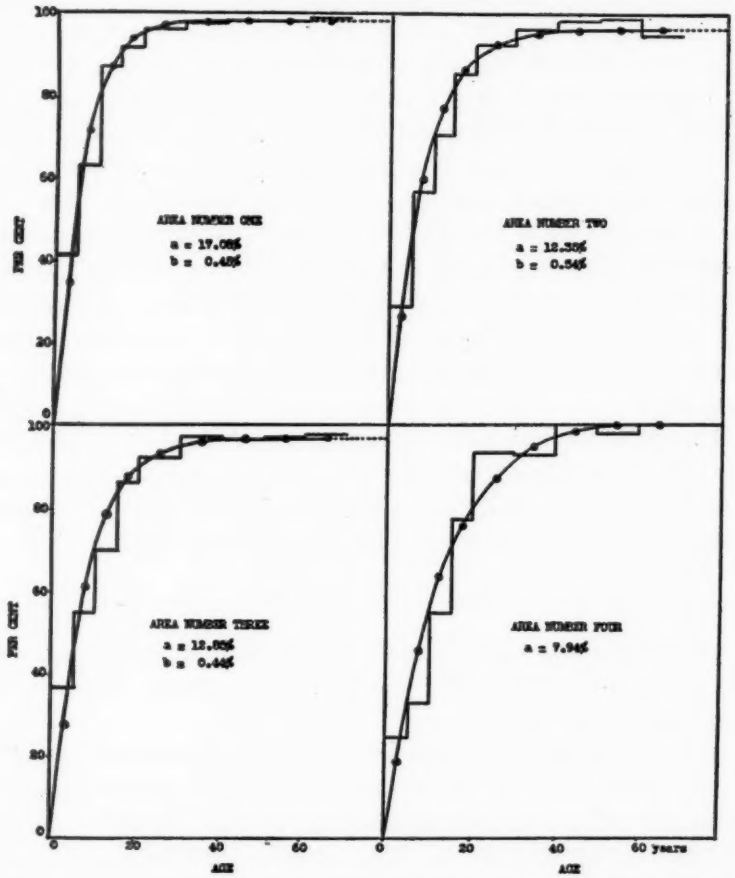

CHART 1. Per cent positive tuberculin reactions by age and areas for both sexes and all colors, with fitted catalytic curves (*cf.* table 1).

spond with a positive reaction to the tuberculin test. This element in the population is found largely in the lower age-groups. With opportunities existing for infection, younger members of the population are exposed more and more from year to year, and consequently are likely eventually to become positive reactors. The catalytic curves presented

Corrected to standard population..... 87.5 82.4 83.5 78.7

in chart 1 portray this annual positive rate of increase in the tuberculin positive reactors (acquisition rate) for each area. These rates were found to be:

	per cent		*per cent*
Area 1	17.08	Area 3	12.85
Area 2	12.35	Area 4	7.94

These rates strongly suggest a difference between area 1 and the others, especially area 4, in the various factors influencing exposure to tuberculosis. Some definite factor or factors must be operating actively in area 1 and less so in area 4 to produce the marked difference in the acquisition rates indicated above. Certain of these have been noted, namely a higher level of manifest tuberculosis, overcrowding, an excess of blacks and dark browns in the population and a definitely lower economic level in area 1. These factors, while present to a degree in areas 2 and 3, are less prominent than in area 1, and thus probably account for the intermediate position of the calculated acquisition rate for these areas.

Synchronously with an annual increase in the proportion of positive reactions, there occurs a loss in the positive response to the tuberculin test among at least a small part of the population. This also has been calculated for three of the areas, with the following results:

Area 1, 0.45 per cent Area 2, 0.54 per cent Area 3, 0.44 per cent

Some difference was found in the proportion of positive reactions for males and females in respective areas. In no instances, however, were these differences significant.

In order to compare the results in Kingston with those obtained by a number of other investigators, chart 2 has been prepared, showing the percentage of positive tuberculin reactions by age. It will be observed that the curves for Kingston are more or less typical for an urban population, which has experienced a fairly high degree of tuberculization.

There are a number of investigations dealing with the level of tuberculous infection in the colored race to which reference should be made. An important paper on tuberculous infection is that published by Opie and his associates (1). The study has to do with subjects of school-age only, who represent, however, an urban population and the results for the ages concerned are comparable with our findings. Reference to chart 2 will show how closely the results agree, and tend to confirm the

opinion resulting from our study that the urban population in Kingston, Jamaica, even during childhood, has attained a high degree of tuberculization.

An interesting contribution to the epidemiology of tuberculous infection is found in the report of the Tuberculosis Research Committee, concerning tuberculosis in South African natives (3). Of special note are the results of tuberculin tests of the inhabitants in Kraals in the southern areas of the Transkeian territories. The inhabitants of these

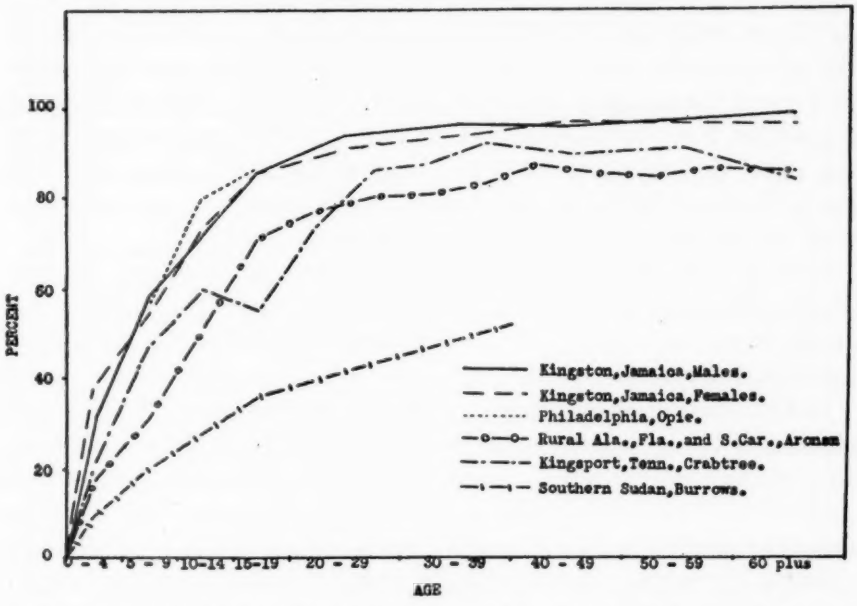

CHART 2. Per cent tuberculin-positive by age and sex for combined areas of Kingston tuberculosis survey, and by age for results of several other investigators.

areas are of the Bantu race, and may be described as negroid rather than negro, many being light brown. There is a constant migration of the adult male population to and from the gold mines of South Africa; those returning not infrequently bringing with them tuberculosis, which tends to explain the high degree of tuberculization found by tuberculin-testing. Using the intracutaneous test of 0.1 cc. of 1–5,000 dilution of O. T., it was found that in the age-group, 0–4 years, approximately 30 per cent gave a positive reaction, the percentage rising rapidly to approximately 93 per cent for age-group, 20–24 years. These findings are in close accord with the results in Kingston, Jamaica, and those

reported by Opie. The subjects tested who lived in Kraals represented a semiurban population, living in close proximity, thus favoring the spread of infection.

Matthews (4), using 0.1 cc. of 1–1,000 and 1–5,000 O. T., tested 683 individuals from 0 to 40-plus years of age in the town of Zanzibar. Except for the lower groups, 0–14 years, the per cent positive was strikingly low when compared to other urban populations, and having in mind the intimate contact for centuries of Zanzibar with other countries.

Burrows (5), employing 0.1 cc. of 1–5,000 solution of O. T., tested 3,662 natives known as Dinkas, living in Southern Sudan. Contact of the outside world with the Dinkas is of relatively short duration, beginning about the middle of the last century. The tribe, with its scattered population, lives a seminomadic life, and tuberculosis as a disease among the tribe was unknown until a comparatively recent date, with the result that tuberculization, as revealed by the results of the tuberculin test, has not developed to a high degree (chart 2).

Wilcocks (6) tested 1,037 natives of all ages of the Bantu race in Tanganyika, employing 0.1 cc. of 1–5,000 dilution of O. T.; 47.9 per cent of all tested were positive. The results are those which would be expected for a rural population.

Notable investigation has been conducted by Aronson (7) (8) on the amount of tuberculous infection among rural Negroes in the southern part of the United States. The technique employed by Aronson was similar in all essential details to that used in Jamaica, and thus the findings are comparable. Testing 524 individuals of all ages in Lake County, Tennessee, produced results strikingly high for a rural population, although the per cent positive up to ages 20–29 years was approximately 10 points below that obtained in Kingston. A similar study included subjects from four counties in Alabama, two in Florida, and one in South Carolina, the average density of the population being something less than 30 per square mile. More than 12,000 individuals, representing all ages, were tested. The results are shown in chart 2. It will be noted that the percentage positive for all age-groups is appreciably lower than that found in Kingston but, nevertheless, it indicates a fairly high degree of tuberculization. Of more than passing interest was the finding by Aronson, that the white population in the respective areas on the whole showed a lower tuberculin-positive percentage than was found for the colored population.

Crabtree, Hickerson and Hickerson (9) studied the results of the

tuberculin test in 525 Negroes living in Kingsport, Sullivan County, Tennessee, representing all ages. Their technique was similar to that employed by Aronson; their results are shown in chart 2. The findings are those which one might expect in an urban community; Kingsport is a town of approximately 15,000 population. The positive percentages were only slightly lower than those found in Kingston, Jamaica.

2: Tuberculin Reaction in Relation to Color

An analysis of the results of the tuberculin test on the basis of color failed to disclose significant differences. For purpose of record, findings for the four areas are consolidated and given below.

Opie and his associates (1) in Philadelphia, testing 1,507 colored and 2,600 white children from 3 to 20 years of age, found no significant difference in the percentages of tuberculin-positive reactions. The same group, considered by sex, showed a slightly higher level for girls, but the difference was not significant.

Aronson (7) (8) found a significant difference in the tuberculin reactions among white and colored subjects living under similar rural conditions. Among school-children in Gibson County, Tennessee, aged 5 to 19 years, he reported 54.2 per cent positive for 786 whites and 63 per cent for 244 colored subjects; and in rural Alabama, Florida and South Carolina for 5,454 colored males, 6,574 colored females, 321 white males and 291 white females tested, including all ages, the results were 62.6, 61, 55.4 and 55.3 per cent, respectively.

Opie and McPhedran (10) explain this difference on the basis that exposure to infection in the case of the colored race is more likely to be characterized by "massive dosage" than is the case with white subjects. On the other hand, Crabtree and his associates (9) in tests applied to white and colored children, ages 5–19 years, in Kingsport, Tennessee, found a significantly lower level for colored.

This report is concerned, not so much with the difference in the tuberculin reaction found in the two races, as with the possibility that racial mixture may cause some difference in the results. Such an effect, however, if present, cannot be demonstrated statistically, although a slight downward trend in the corrected rates was noted from "Black" to "Light Brown" and "Others." On the whole, one is led to doubt if the white race possesses any inherent qualities, inherited or acquired, which, when mixed with other races, may influence the effect of tuberculous infection in so far as such infection is revealed through the tuberculin reaction.

A recent paper by Crouch (11) reports significant differences in the results of tuberculin tests among Indians. His findings were as follows: Full-blooded Indians, 75 per cent positive; mixed with whites—one-fourth or more Indian, 54.3 per cent positive; and mixed with white—less than one-fourth Indian, 39.3 per cent positive. These findings would seem to suggest some racial influence; on the other hand, other factors,

TABLE 2

Per cent tuberculin-positive by age and color: areas and both sexes combined

AGE IN YEARS	PER CENT TUBERCULIN-POSITIVE			
	Black	Dark brown	Light brown	Others*
0–4	35.4	32.2	36.4	41.4
5–9	59.8	53.8	51.9	52.4
10–14	75.0	77.9	64.6	63.0
15–19	86.4	89.6	80.8	87.0
20–29	93.8	93.3	94.0	91.8
30–39	97.7	96.2	96.2	88.7
40–49	98.2	97.2	99.0	94.3
50–59	97.2	99.0	97.5	93.8
60 plus	94.6	96.4	100.0	100.0
Total.....	84.4	81.3	79.5	79.4
Per cent positive corrected to standard population.....	84.8	84.7	83.0	81.1

* The group designated "Others" included East Indians, Chinese, Whites, and Syrians; 316 individuals were tested; the number, however, is too small to lend itself to further analysis under each class.

such as housing and living habits for each group must be considered and weighed before accepting the above inference.

3: The Intensity of the Tuberculin Reaction

It is probable that several factors play an important rôle in determining the degree of reaction which will result when tuberculin is brought into intimate contact with the body-cells. Our knowledge of the phenomenon of the tuberculin reaction, although rather extensive, is still too incomplete to offer a full and satisfactory explanation of all the variations in the reaction. Within certain limits, however, there does appear to be some association between the intensity of the positive

reaction and the extent of involvement, brought about by infection and disease.

Our interest at this point is not primarily to settle the above question, but rather to analyze the results of the tuberculin test in respect to intensity in the four survey areas, and to compare such differences as were observed. For the purpose of comparison, the results for areas 1 and 2 have been combined, and also those for areas 3 and 4. This arrangement is logical on the basis of social and economic conditions prevailing in the respective areas and to a somewhat lesser degree from the standpoint of color. The data are shown in table 3 and graphically in charts 3a and 3b. In each group it will be observed that the proportion of one-plus reactions to 0.01 mgm. for each age was approximately the same, with one exception, namely, that for individuals 60 years old and over, in areas 3 and 4. Areas 3 and 4 showed a higher percentage of one-plus reactions for every age than was found in areas 1 and 2. This excess appears to be associated largely with a loss in percentage of two-,

TABLE 3

Distribution of intensity of tuberculin reactions by age: comparing areas 1 and 2 with areas 3 and 4

AGE IN YEARS	AREAS ONE AND TWO								AREAS THREE AND FOUR							
	1.0 mgm.		0.01 mgm.						1.0 mgm.		0.01 mgm.					
			One plus		2, 3 and 4 plus						One plus		2, 3 and 4 plus			
	Number Positive	Per cent of Total Positive	Number Positive	Per cent of Total Positive	Number Positive	Per cent of Total Positive	Total Number Positive	Per cent of Total Positive	Number Positive	Per cent of Total Positive	Number Positive	Per cent of Total Positive	Number Positive	Per cent of Total Positive	Total Number Positive	Per cent of Total Positive
0–4	48	39.0	49	39.8	26	21.2	123	100.0	22	31.4	36	51.4	12	17.1	70	99.9
5–9	77	36.0	71	33.2	66	30.8	214	100.0	30	25.0	66	55.0	24	20.0	120	100.0
10–14	49	23.8	77	37.4	80	38.8	206	100.0	26	16.6	89	56.7	42	26.7	157	100.0
15–19	56	19.5	105	36.6	126	43.9	287	100.0	45	19.6	124	54.1	60	26.2	229	99.9
20–29	127	14.4	326	37.0	429	48.6	882	100.0	61	10.6	303	52.6	212	36.8	576	100.0
30–39	54	11.7	175	37.9	233	50.4	462	100.0	21	7.2	145	50.0	124	42.8	290	100.0
40–49	35	13.7	99	38.7	122	47.7	256	100.1	10	5.6	97	54.8	70	39.6	177	100.0
50–59	27	17.8	60	39.5	65	42.8	152	100.1	10	6.9	81	56.3	53	36.8	144	100.0
60+	20	22.5	37	41.6	32	35.9	89	100.0	6	5.3	81	71.7	26	23.0	113	100.0
Total	493	18.5	999	37.4	1,179	44.1	2,671	100.0	231	12.3	1,022	54.5	623	33.2	1,867	100.0

excess appears to be associated largely with a loss in percentage of two-,

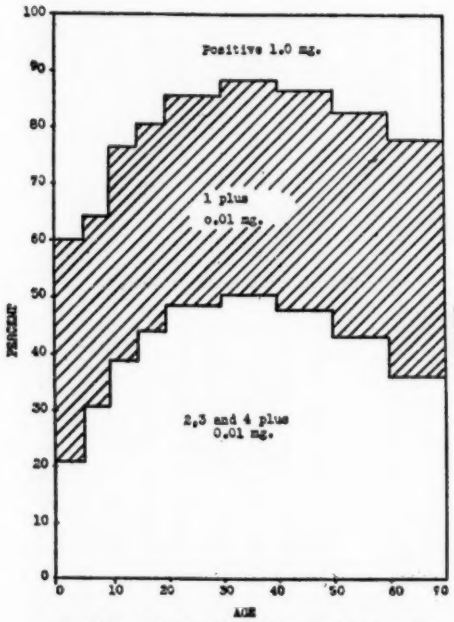

CHART 3a :- Distribution of Intensity of Tuberculin Reactions, by age, for Areas Number 1 and 2.

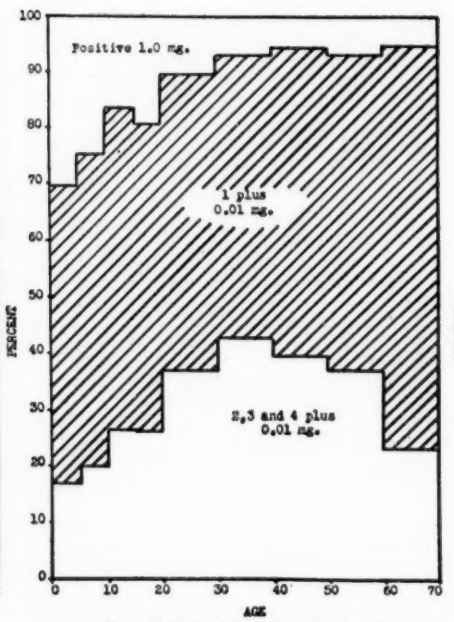

CHART 3b :- Distribution of Intensity of Tuberculin Reactions, by age, for Areas Number 3 and 4.

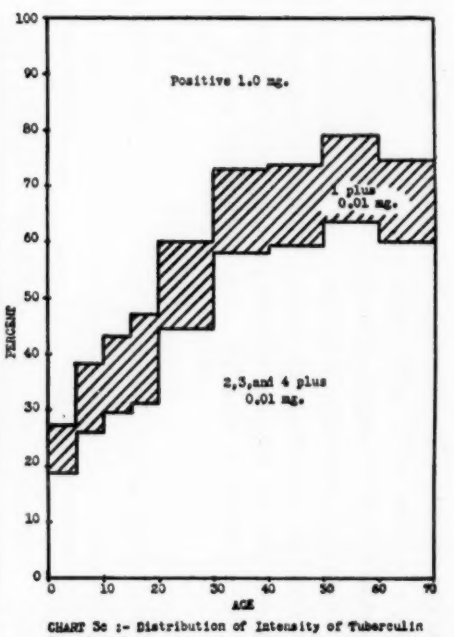

CHART 3c :- Distribution of Intensity of Tuberculin Reactions, by age, for colored subjects, Southern United States, Aronson.

three-, and four-plus reactions for all ages, and a loss in percentages of positive reactions to 1 mgm. after 30 years of age. No satisfactory explanation can be advanced for these findings.

The duration of residence in Kingston has been determined for all reactors, but no significant difference in this regard was found for any of the areas. Social, economic, hygienic, and sanitary conditions, as well as color, differ materially in the two groups of areas, and it may be that these influences are capable of and do affect the opportunities for massive contagion sufficiently to produce the differences observed.

With regard to the more severe reactions, two-, three-, and four-plus to 0.01 mgm., the same general trend is found in both groups, although the findings for areas 1 and 2 show a higher percentage of such reactions for every age, and suggest greater opportunities for massive infection. In this connection it should be noted that the level of manifest tuberculosis was 1.68 per cent in areas 1 and 2 and 0.99 per cent in areas 3 and 4.

The same trend with respect to the percentages of positive reactions to 1 mgm. up to 40 years of age was observed in all areas. After 40 years of age there was a gain in the percentages of these reactions in areas 1 and 2, and in areas 3 and 4 a loss. This variation is probably associated with the factors noted above.

References in the literature to the intensity of the tuberculin reaction are largely concerned with the relation of the severer reactions to demonstrable, active or latent lesions. This aspect of the subject is of considerable interest, and merits further discussion on the basis of our data. This will be reserved, however, for a future report.

One reference, bearing on the distribution by age of intensity of the tuberculin reaction, lends itself to comparison with the Kingston results. Aronson (8) tested 12,028 colored persons living in several Southern States. Chart 3c has been prepared from his data, and, when compared with the Kingston results, it shows a number of striking differences. Aronson found a comparatively low ratio of one-plus reactions to 0.01 mgm., the proportion being almost identical for each age-group, and in this respect agreeing closely with the Kingston results. The proportion of his reactions to 1 mgm. was appreciably higher for every age-group, as were likewise the two-, three-, and four-plus reactions to 0.01 mgm., for all ages over 30 years. For ages 0–30 years, his proportion of severe reactions was lower. Unfortunately, Aronson does not include in his study an investigation as to the amount of manifest tuber-

culosis in the population tested. We are inclined to believe that this must have been significantly lower than in the Kingston material. If so, this factor, associated with a scattered population of less than 30 per square mile, may be advanced as an important influence in bringing about the differences noted above.

4: The Tuberculin Reaction in Relation to Age and Length of Residence in Kingston

The population of Jamaica is largely rural, the urban population being confined to Kingston and St. Andrew, estimated at something under 125,000. There are about a dozen other towns varying in population from 1,000 to 12,000. Approximately 15 per cent of the island population may therefore be considered urban and the remaining 85 per cent typically rural. In Kingston and the larger towns, the native population lives under extremely crowded conditions, in small ill-ventilated rooms, a large number of rooms often gathered together in a single yard. In the country districts, although some crowding may prevail, it is customary for each family to have its own house, with one or more small rooms, and often with a small plot of land. The majority of the country people have never visited the metropolis, Kingston, although once a week or less frequently on market days they may visit the nearest town. Direct, intimate, or sustained contact, therefore, between the country and city populations is reduced to a minimum and should be reflected to some degree in the amount of tuberculous infection found among the rural inhabitants. The influence of this factor is partly offset by the prevailing custom of a tuberculosis patient, after acquiring his disease in the city, to return to his old home in the country to pass his last days: this results in some spread of tuberculosis in the country parts. Again, while there is a distinct line of demarcation between the rural and urban populations in Jamaica, additional contact is favored because of considerable migration of young adults of both sexes, especially females, from the country to Kingston. This is largely due to greater opportunities for work and better wages and a demand for servants in the homes of the better class. Unfortunately, even if service of this nature is obtained in the city, the individual must often seek living-quarters away from the home of his or her employer; such quarters are almost universally in the poorest and most congested sections of the city. Because of these conditions some interest is attached to an analysis of the results of the tuberculin test in relation to the length of

TABLE 4

*Positive tuberculin reactions in relation to age and length of residence in Kingston, for areas 1, 2 and 3**

AGE IN YEARS	LENGTH OF RESIDENCE IN KINGSTON, IN YEARS				
	0–1	1–4	5–9	10–19	20 plus
	Per cent positive				
0–4	28.0	39.6			
5–9	50.0	57.4	59.7		
10–14	70.7	60.3	83.3	78.5	
15–19	75.7	81.7	90.0	92.9	
20–29	92.1	88.9	94.1	95.8	94.6
30–39	93.8	98.8	95.0	96.5	97.4
40–49	96.2	97.2	100.0	100.0	96.0
50–59	81.8	100.0	94.4	97.3	98.8
60 plus	85.7	100.0	93.3	100.0	97.4

* Area 4 is omitted because it has a stable and better class of population.

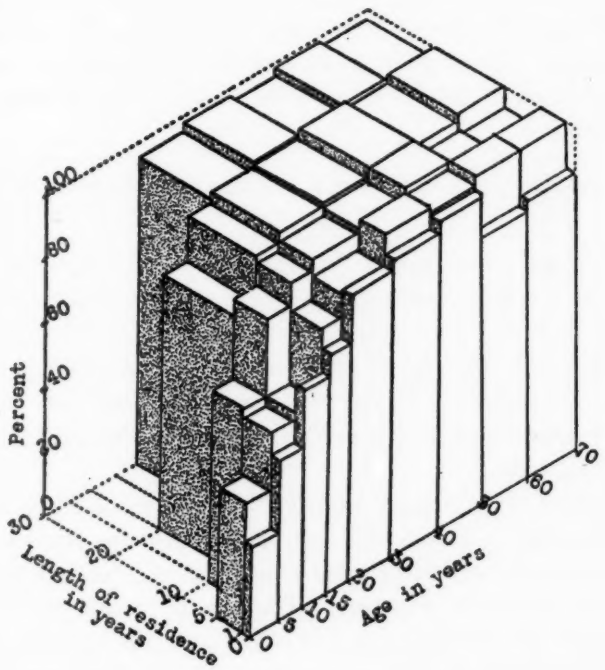

CHART 4. Per cent positive tuberculin reactions in relation to age and length of residence in Kingston for areas 1, 2 and 3.

residence in Kingston; the data covering this relationship are given in table 4, and shown graphically in chart 4. The findings for all ages 20 years and over coincide with those expected in adults living in large cities; the percentages of positive reactions are all at a high level, with the exception of those 50 years of age and over, living in Kingston one year. This finding may possibly be disregarded, because of the small number of individuals in this category. In the case of individuals under 20 years of age, there appears to be a definite correlation between the percentages of positive tuberculin reactions and the length of residence in Kingston, the latter factor representing an increased opportunity for contact with open cases of tuberculosis under conditions decidedly favorable for acquiring infection. In the older age-groups, 20 years and over, one might expect a lower tuberculin-positive level with shorter residence in the city. This is not necessarily the logical conclusion; for older individuals, even though living in the country most of their lives, have probably had opportunity for casual or minimal exposure to tubercle bacilli through occasional visits to the city, or by contact with cases of tuberculosis returning from the city to their homes in the country. Such contact is materially aggravated by the absence in most instances of any effective control measures or supervision of positive cases.

5: Tuberculin-Positive Reactions in Relation to History of Contact with Tuberculosis

So-called mass investigation by means of the tuberculin test has, during recent years, thrown much light on many formerly perplexing questions involved in the tuberculosis problem. Particularly is this true with respect to the rôle of contagion as against heredity in the production of tuberculosis. The expression "phthisical" or "tuberculous family" now takes on a new meaning, as does likewise the designation "tuberculous dwelling."

An analysis of the Kingston survey material corroborates the conclusions of other investigators that, the more intimate the contact with open tuberculosis, the greater will be the level of infection, as indicated by a positive tuberculin reaction. The results of this relationship are shown in table 5. The findings have been divided into 6 classes, which should theoretically reflect varying degrees of exposure to infection.

Primary cases are not included in the table or the calculations. Total percentages for each class have been corrected to a standard population,

TABLE 5

The results of tuberculin test and history of contact with manifest pulmonary tuberculosis
(Manifest cases omitted in calculations)

AGE IN YEARS	SEX	PRESENT HOUSEHOLD SPUTUM-POSITIVE			PRESENT HOUSEHOLD SPUTUM-NEGATIVE			FORMER HOUSEHOLD			PRESENT EXTRA-HOUSEHOLD			FORMER EXTRA-HOUSEHOLD			NO CONTACT KNOWN		
		Number Tested	Number Positive	Per cent Positive	Number Tested	Number Positive	Per cent Positive	Number Tested	Number Positive	Per cent Positive	Number Tested	Number Positive	Per cent Positive	Number Tested	Number Positive	Per cent Positive	Number Tested	Number Positive	Per cent Positive
0–9	M	10	10	100.0	10	4	40.0	20	13	65.0	44	22	50.0	34	21	61.8	453	188	41.5
	F	6	4	66.7	11	5	45.5	19	11	57.9	46	30	65.2	25	15	60.0	481	204	42.4
10–14	M	3	3	100.0	4	4	100.0	4	4	100.0	18	12	66.7	13	13	100.0	183	126	68.9
	F	3	3	100.0	3	2	66.7	4	4	100.0	18	18	100.0	12	12	100.0	236	162	68.6
15 plus	M	13	13	100.0	30	28	93.3	24	24	100.0	95	88	92.6	78	77	98.7	1,072	1,017	94.9
	F	26	25	96.2	45	42	93.3	55	55	100.0	173	164	94.8	112	110	98.2	2,106	1,951	92.6
Total		61	58	95.1	103	85	82.5	126	111	88.1	394	334	84.8	274	248	90.5	4,531	3,648	80.5
Percentages corrected to standard population				96.7			84.5			93.3			86.8			92.3			82.2

using for that purpose the population of Kingston as a whole. The highest positive level, 96.7 per cent, was found for individuals in "Present Household" contact with sputum-positive cases. For "Former Household" contacts, the level was 93.3 per cent, while for "Former Extra Household" contacts, 92.3 per cent. Compared to the above were "Present Extra Household" contacts, 86.8 per cent; "Present Household Contacts—sputum-negative," 84.5 per cent; and those for whom "None Known" contact was obtained, 82.2 per cent. The results are those to be expected, with the highest level for those in contact with sputum-positive tuberculosis. "Former Household" and "Former Extra Household" both show a high frequency, and suggest that the past contact was with a sputum-positive individual. The "Present Extra-Household" class gave a higher level than "Present Household—sputum-negative," and may be explained on the basis that, in the "Present Extra-Household" group, no allowance was made for sputum-positive and sputum-negative cases. Except for the "Unknown" contact group, the lowest positive percentage was obtained for "Present Household—sputum-negative." These findings suggest that contact with a persistently sputum-negative case does not offer the serious degree of danger of infection encountered in contact with a sputum-positive individual.

Similar conclusions with respect to the importance of contagion are found among recent reports in the literature, some of which are worthy of note. All of the investigations to which reference is made were based on the intracutaneous tuberculin test for determining infection. Opie and McPhedran (10) in Philadelphia made a careful study of the spread of infection among 272 children exposed to a sputum-positive case of tuberculosis in the same household. They found a tuberculin-positive percentage of 80 for ages 0–5 years, rising to 100 per cent positive at age 20, and among 179 no-contact controls, a positive level of 23 per cent for ages 0–5 years, rising to 100 per cent at age 20 (see chart 5).

Allan (3) found among colored families 81 per cent of positive reactions in tuberculous families, and 57 per cent positive in nontuberculous families.

Schlesinger and Hart (12), studying a group of London children of the hospital class, 0–15 years, found a positive level of 62 per cent among home-contacts to tuberculosis and 24 per cent positive in a noncontact control group of similar ages (see chart 5). Subdividing the contact group, 0–10 years, further revealed the following significant positive

frequencies: bedroom-contacts to open pulmonary tuberculosis, sputum-positive, 71 per cent; home-contacts of open pulmonary tuberculosis, sputum-positive, 69 per cent; home-contacts of open pulmonary tuberculosis, sputum-negative or unknown, 42 per cent; home-contacts of nonpulmonary tuberculosis, 15 per cent; and noncontact controls, 18 per cent.

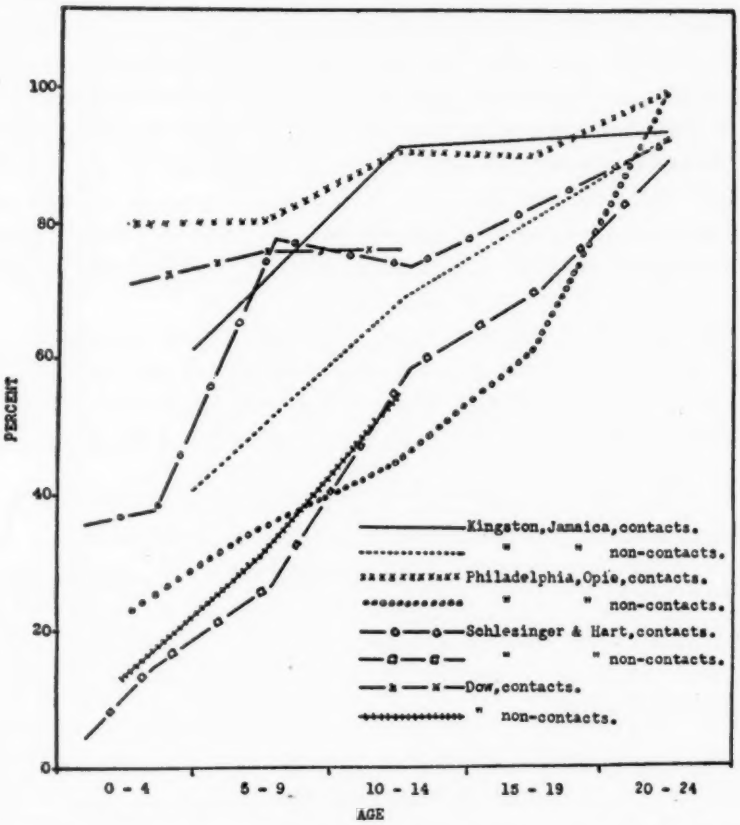

CHART 5. Showing results of tuberculin tests, by age, for persons in contact with tuberculosis and those for whom no contact is known.

Dow and Lloyd (13), studying an urban working-class population, tested 184 contacts with sputum-positive tuberculosis, 95 contacts with sputum-negative tuberculosis and 724 no-contact controls, all subjects being children, 0–15 years of age. Their results showed sputum-positive contacts, 75.5 per cent positive; sputum-negative contacts, 36.8 per cent positive; and the no-contact controls, 35.6 per cent positive (chart 5).

That the higher positive tuberculin level in the above studies is not something peculiar to urban conditions and possibly influenced by such conditions, is indicated by the following investigations among rural populations:

Aronson (7) reported the results of tuberculin tests in Sunflower County, Mississippi. For Negroes on two plantations, known to be harboring manifest tuberculosis, positive ratios of 74.3 and 74.2 per cent were obtained for all ages, although the great majority of subjects were under 24 years of age. For Negroes on a third plantation, on which no cases of tuberculosis were known, 54.7 per cent positive reactors were found; and for tests on a white population living under similar conditions and without known contact with tuberculosis, a ratio of 54.8 per cent.

Korns (14) tested 244 subjects, 0–19 years of age, in contact with sputum-positive cases of tuberculosis, and found 65 per cent positive. His control group of 2,394 noncontacts gave 11 per cent positive reactions.

Crabtree and his associates (9), testing 107 persons in contact with manifest tuberculosis and 418 controls, found 75.6 per cent positive among the contact group and 60.7 per cent for the control. Approximately half of those tested for both groups were under 20 years of age.

6: The Results of Tuberculin Test in Relation to Occupation

The results of the tuberculin test in relation to occupation have been studied in this investigation. The findings were not significant, although indications were present, after proper corrections had been made for age distribution, that dressmakers, laborers, housewives and domestics gave evidence of more exposure than clerks, independents and a miscellaneous group.

7: The Results of Tuberculin Test in Relation to Size of Household and Number of Individuals per Room

The number of persons in a household or family is not necessarily indicative of overcrowding. That crowding plays a considerable rôle in the spread of tuberculous infection has been strongly emphasized. An analysis of our data, on the basis of size of household, failed to disclose any significant differences in the level of positive reactors for households of different sizes. On the other hand, when considered from the standpoint of crowding or the number of individuals per room, a distinctly different picture was found. These results are tabulated in table 6.

In order to determine whether the apparently regular increase in positive percentages, with an increase in the number of persons per room in the two younger age-groups was significant, the correlation coefficient has been calculated, with the following results:

"r" biserial for 0– 9 years : + 0.0780 ±.0248 (P = 0.03)
"r" biserial for 10–14 years : + 0.2172 ±.0388 (P = 0.0002)
"r" biserial for 15 plus years: + 0.0519 ±.0214 (P = 0.1)

That a definite correlation exists between crowding and positive tuberculin reactions in the age-group, 10–14 years, is evidenced by the high value of "r"; for the age-group, 0–9 years, the correlation is very slight

TABLE 6

Relation of positive tuberculin reactions to the number of persons per room, for all areas

AGE IN YEARS	PER CENT TUBERCULIN POSITIVE							
	Number of persons per room							
	0–0.9	1–1.9	2–2.9	3–3.9	4–4.9	5–5.9	6–6.9	7 plus
0–9	31.8	38.5	47.8	45.9	45.4	46.0	48.8	53.3
10–14	57.1	61.5	66.0	80.6	84.3	80.0	66.7	86.2
15 plus	92.6	92.2	94.5	95.9	94.6	92.5	95.5	94.0

but possibly significant, while in the 15-plus-years group no correlation is found. This might be expected, since adults, who largely make up this group, living under urban conditions, normally show a high positive tuberculin percentage. The values for "P" which have been calculated, are shown, since they express the probability of obtaining so high a value of the correlation coefficient by accident. These data and calculations lead to the conclusion that the tuberculin-positive ratio changes significantly and regularly with increased crowding in the younger age-groups, and that this change is one to a higher positive level with increased crowding.

It would be desirable to extend this inquiry to the effect, on the number of tuberculin reactors, of various degrees of crowding in tuberculous and nontuberculous households. Such analysis of our material is prevented by the small number of individuals in the sputum-positive households.

SUMMARY AND CONCLUSION

As a part of an epidemiological study of tuberculosis in Jamaica, tuberculin tests were made on 5,554 individuals living in four separate sections of the city of Kingston, and representative of the different economic and social elements in the general population. The results, when considered as a whole, resemble the picture reported by others for urban populations; this was particularly true for three areas.

In area 4 the percentage positive for individuals under 20 years of age was significantly lower. This finding is explained on the basis that the population in area 4 was distinctly of the better class in every respect; overcrowding was absent and, incidentally, the level of manifest tuberculosis was materially lower than in the other areas. The greatest difference in the proportion of positive reactors was noted between area 1, a densely populated section of the city, peopled almost entirely by the poorest and most ignorant class, and area 4. This difference found reflection also in the annual rate of increase of the tuberculin-positive reaction, 17.08 per cent for area 1 and 7.94 per cent for area 4.

The population in three areas was predominantly black and dark brown; the percentage being, area 1, 87.5 per cent; area 2, 76.9 per cent; and area 3, 53.4 per cent; whereas, in area 4, only 44 per cent belonged to these groups. The remaining population in each area comprised largely light and pale brown persons and others. No significant difference was found in the positive tuberculin reactions in relation to color, although a slight downward trend was noted in the corrected percentages from "Black" to "Others."

Combining the results of the tuberculin test on the basis of similarity in economic, social, color, and other conditions, namely, areas 1 and 2 as one group and areas 3 and 4 as a second, brought out certain differences with regard to the intensity of the tuberculin reactions. Areas 1 and 2 showed a higher proportion of the more severe tuberculin reactions, classified as two-, three- and four-plus to 0.01 mgm., and showed a smaller proportion of reactions designated as one-plus to 0.01 mgm. Areas 1 and 2 gave a somewhat greater proportion of positive reactions to 1 mgm. Associated with these findings should be mentioned the level of manifest pulmonary tuberculosis, 1.68 per cent for areas 1 and 2, and 0.99 per cent for areas 3 and 4. We are inclined to believe that these proportions reflect the opportunity for massive infection in the respective areas, and thereby have a direct influence on the proportion of the severe reactions, two-, three- and four-plus to 0.01 mgm. which

were found, and at least partially explain the differences noted. While the excess in one-plus reactions to 0.01 mgm. for areas 3 and 4 should be noted, it may be that this degree of reaction is of less significance than the more severe types.

The amount of manifest or active tuberculosis is decidedly greater in Kingston than in the country parts of Jamaica, the natural corollary being that opportunity for infection, thereby acquiring a positive tuberculin reaction, is much less in the rural parts than in the metropolis. Corroboration of this inference has been determined.[3]

Many of the country folk are attracted to Kingston, where in many instances they encounter tubercle bacilli for the first time; especially is this true for those under 20 years of age. This study has shown for all age groups, 0–20 years, a consistent increase in positive tuberculin reactions with length of residence in Kingston. The positive level for those of all ages residing in Kingston less than one year was consistently lower than that obtained for the combined population of all four survey areas, although somewhat higher than that obtained in rural parts. This difference probably indicates the degree of greater opportunity for infection during residence in Kingston, even for as short a period as one year or less.

Every tuberculin-positive reaction represents contact with tubercle bacilli, discharged from some individual, the victim of active disease; on the other hand, it does not necessarily follow that every individual in contact with an active case takes into his system a sufficient quantity of tubercle bacilli to produce sensitization. However, this study, as well as investigations by others, demonstrated that a higher percentage of individuals in home contact with sputum-positive cases developed a positive tuberculin reaction than in the case of individuals for whom no such intimate contact was known. Additional evidence is thus furnished, indicating the grave danger of infection, which may lead to disease, incurred by those in household or intimate contact with sputum-positive cases of tuberculosis.

Occupations involving dust hazards are practically unknown in Jamaica; consequently, one would not expect to find from an analysis of our data any striking or significant correlation between occupation and the results of the tuberculin test. Other factors, such as crowded and ill-ventilated rooms which might favor the spread of infection, are

[3] Personal communication from Dr. E. W. Flahiff, who has undertaken a tuberculin survey of rural parts of Jamaica.

not usually encountered as a part of any local occupation. Unsanitary and unhygienic habits among the poorer classes are no more in evidence at work than in the home, and certainly are not associated in any appreciable degree with any particular occupation.

This study failed to demonstrate any increase in the tuberculin positive ratio with increase in the size of families; if anything, the converse was shown, for in area 1, with families averaging 2.79 persons, there was a definitely higher level of positive reactors than in area 4, with 4.94 persons per family. We are, therefore, not convinced that the size of the family *per se* is an essential contributing factor in determining the results of the tuberculin test. On the other hand, the factor of crowding, as determined by the average number of persons per room, showed a definite and significant association with the results of the tuberculin test in individuals under 15 years of age.

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THE INCIDENCE OF TUBERCULOSIS IN CHILDREN ENTERING PRIMARY SCHOOLS IN VANCOUVER, BRITISH COLUMBIA

An Attempt to Trace Their Sources of Infection with a Suggested New Approach to Case-Finding[1, 2]

A. R. J. BOYD[3]

This study was primarily undertaken to determine the feasibility of examining whole families, in an effort to explain the occurrence of tuberculous infection and demonstrable tuberculous lesions in a group of children; and second, to evaluate the findings from the standpoint of their application in new methods of case-finding.

The first step was the selection of the group of children with which to commence the work. It was considered that the primary class of the schools would be the most promising, in that home-contacts are probably responsible for their infection more frequently than is the case in older children. A further selection within the group was necessary. For this purpose a tuberculin survey of the primary class was undertaken. Still further selection was made by the examination of the positive reactors.

The following report will be divided into two parts, the first dealing with the findings in the children of the primary class, the second with the findings in the families in which the school beginner has been infected with the tubercle bacillus.

PART 1

The Incidence of Tuberculosis in Children Entering Primary Schools

Tuberculin-testing of the children in the public schools of the City was begun in October, 1934, and completed for the primary class in November, 1934. The positive reactors were examined at the Clinic during November and December, 1934, and January, February and March of 1935.

An attempt was made to obtain consent for examination of all the receivers in the 53 primary public schools of the City. Shortly after

[1] From the Vancouver Public Health Institute for Diseases of the Chest, Vancouver, British Columbia.

[2] Prize-winning thesis in the 1935 competition conducted by the Canadian Tuberculosis Association.

[3] Kinsman Fellow in Tuberculosis.

the beginning of the school-year a pamphlet describing the requested examination, together with a consent form, was given to each child in the primary class to take home.

Of a total receiving class of 2,248 children, consent to examine was obtained for 1,255, or 55.82 per cent. All tests were made and read, by the writer, in the schools. The intracutaneous (Mantoux) test was used throughout. An initial injection of 0.1 cc. of a 1–1,000 dilution of O. T. was made. Negative reactors were given a "repeat" test, using 0.1 cc. of a 1–100 dilution of O. T. The tuberculin used was prepared and standardized according to international requirements by Connaught Laboratories, Toronto. Dilutions were prepared freshly each day. No phenol was added. No control injections were made. Work in this Clinic has shown that no reaction occurs to the injection of physiological saline solution into the skin. Dickey and Seitz (1), who found that a saline-solution control produced no reaction, discontinued its use.

At the time of visiting the various schools, 112 children were absent. One thousand, one hundred and forty-three children received the first injection; of these, 61 reacted positively. Consent to examine was withdrawn for three children after the first injection. They were negative reactors. One thousand and seventy-eight children were given the "repeat" test; 166 had positive reactions. In all, 227, or 19.86 per cent, of the group were positive reactors.

Of 35 children five years old, 5, or 14.28 per cent, had positive reactions; of 89 seven-year-old children, 17, or 19.10 per cent, reacted; 5, or 27.77 per cent of 18 children over seven years of age had positive reactions. The remaining 1,001 children were six years of age. Of these, 518 were boys and 483 girls. The group comprised 857 children of the white race, 110 Japanese, 29 Chinese, 3 East Indians, and 2 Negroes. Two hundred and one, or 20.08 per cent, had positive tuberculin reactions.

TABLE 1

	1/1000 DILUTION			1/100 DILUTION			TOTAL		
	Number	Positive	Per cent	Number	Positive	Per cent	Number	Positive	Per cent
Male	518	28	5.40	474	73	15.40	518	101	19.49
Female	483	24	4.96	443	76	17.15	483	100	20.70
Total	1,001	52	5.19	917*	149	16.24	1,001	201	20.08

* 32 children did not receive or were absent for the reading of the "repeat" injection.

Table 1 gives the results of the skin test for sex and shows the percentage of reactors for each amount of tuberculin injected. It is of interest that the percentage of reactors to the first injection was very low. Three-quarters of all reactors were negative to 0.1 cc. of 1–1,000 dilution of tuberculin. This does not correspond with the findings of most workers, although Hetherington, *et al.* (2) found in one school less than half the total reactors sensitive to the smallest dose of tuberculin used. However, they began with 0.01 mgm., and repeated the test in negative reactors with 0.1 and 1.0 mgm. of tuberculin. Harrington and Myers (3) report less difference between the number of reactors to weak and strong dilutions of tuberculin than most reports show.

Very little difference is apparent between the percentage of positive reactions among boys and girls. Dickey and Seitz (1) report a similar small excess of positive reactions among girls, 17.6 per cent positive among girls and 15.5 per cent among boys. In London, Dow and Lloyd (4) found 41.3 per cent reactors among boys and 48.1 per cent among girls at six years of age. Drolet (5) reports a higher incidence in males than in females at this age. Harrington and Myers (3) report 25.75 per cent of girls and 15.25 per cent of boys with positive skin tests in Minneapolis.

The percentage of children positive to tuberculin skin tests shows a marked variation in reports from different countries, and from different parts of the same country. Part of the variation is probably due to differences in strength of tuberculin used and in amounts injected, as well as in the method of testing. Hetherington, *et al.* (6) found 43.1 per cent positive reactors at six years among school-children in Philadelphia. Johnson and Chadwick (7) report only 12.6 per cent positive at this age in Detroit. Ferguson (8) found 44.4 per cent of six-year-old children in Saskatchewan reacting to the Pirquet test. Baker (9), using the intracutaneous test, found only 6.3 per cent positive among children of the same age in the neighboring province of Alberta.

TABLE 2

	MALE			FEMALE			TOTAL		
	Number	Positive	Per cent	Number	Positive	Per cent	Number	Positive	Per cent
White	436	79	18.1	421	85	20.2	857	164	19.1
Japanese	59	12	20.2	51	12	23.5	110	24	21.8
Chinese	20	9	45.0	9	2	22.3	29	11	37.9
East Indian	2	1	50.0	1	1	100	3	2	66.6
Negro	1	0	0	1	0	0	2	0	0
Total	518	101	19.5	483	100	20.7	1,001	201	20.1

Table 2 gives the variation in percentage of positive reactors for race and sex. It will be seen that the percentage of positive reactors among Japanese is slightly greater than among white children, and that among Chinese it is considerably higher. The Chinese group is small and perhaps the results cannot be considered conclusive for that reason. In the Japanese group the higher percentage of reactors among girls is more marked than among white children. A higher percentage of Chinese boys had positive reactions than girls. Doolittle (10), in a study of the incidence of tuberculosis in various racial groups in Hawaii, concludes that the percentage of infection in different races is probably affected only by the opportunities for contact. Hetherington, *et al.* (6) found no appreciable difference in the percentage of tuberculin-positive children in white and colored children in Philadelphia, where the death-rate in the colored race is higher than in the white.

In Vancover the death-rate in the Oriental races is much higher than in the white race. The rate among Chinese is very much the same as for Japanese. Both Oriental groups, for the most part, live in congested parts of the City in poor and overcrowded homes. Thus the opportunities for infection should be more frequent for the Oriental child than for others. It is difficult to see how they can be more frequent for the Chinese than the Japanese, although there are probably more unrecognized tuberculous individuals among the Chinese than the Japanese. There are on record 5 tuberculous persons in the Japanese population for each Japanese who died from tuberculosis, and 3.6 in the Chinese population for each Chinese who died from tuberculosis in 1933.

TABLE 3

Size of reaction according to race and sex

	WHITE		JAPANESE		CHINESE		TOTAL	
	M	F	M	F	M	F	M	F
For 0.1 cc. of 1–1,000 dilution of O.T.								
+	5	3	1	1	0	0	6	4
++	3	3	1	0	1	0	5	3
+++	8	10	5	6	3	1	16	17
++++	0	0	0	0	1	0	1	0
For 0.1 cc. of 1–100 dilution O.T.								
+	45	50	4	4	2	0	51	54
++	13	13	1	1	0	1	14	15
+++	5	6	0	0	2	0	7	6

Grading of the reactions was done according to the usual method (11). Note that only one four-plus reaction occurred, although the initial injection was 0.1 cc. of a 1–1,000 dilution of O. T. The number of three-plus reactions in those sensitive to 1–1,000 dilution is almost twice the number of two-plus and one-plus combined. Over two-thirds of those reacting to 1–100 dilution had one-plus reactions, while only a small number had three-plus. In general, it was noted that there was less oedema in those showing three-plus reactions to the "repeat" test than those giving three-plus reactions with the greater dilution of O. T.

Table 3 shows a larger percentage of large reactions in Oriental children than in white children. This is in keeping with the findings of Dickey (12), and is probably due to greater opportunity for reinfection in the Oriental races, as he suggests.

TABLE 4

*The relation of weight (per cent of standard) to the tuberculin reaction**

	WHITE				JAPANESE				CHINESE				TOTAL			
	Positive		Negative		Positive		Negative		Positive		Negative		Positive		Negative	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
10 per cent or more under standard weight.....	19	11.8	81	12.1	2	8.3	8	10.4	0	0	3	16.6	21	10.8	92	12.0
9 per cent or less over or under standard weight.	129	81.2	539	80.7	18	75.0	62	80.5	10	90.9	14	77.8	157	80.9	615	80.5
10 per cent or more over standard weight.....	11	6.9	48	7.2	4	16.6	7	9.1	1	9.1	1	5.6	16	8.2	57	7.5

* Based on findings in 958 children.

The percentage of children 10 per cent or more underweight and overweight, and of those within 9 per cent of standard weight, was found to be practically the same for those who reacted to tuberculin as for those who did not react. This is best seen in the large group of white children and in the total groups. In the Japanese and Chinese, underweight children were more frequent among positive than among negative reactors. This may be due to the small numbers considered. In general, the findings agree with those of Hetherington (13), Chadwick (14), and Doolittle (10).

Children who had positive skin tests were given appointments for physical and X-ray examination at the chest clinic. Of 201 positive reactors 189 were examined. The remainder failed to keep their appointments.

TABLE 5

The X-ray findings according to race and sex

	SEX	NUMBER	NEGATIVE	SUSPECTS	POSITIVE	TRACHEOBRONCHIAL	PULMONARY NODULE	TRACHEOBRONCHIAL PULMONARY NODULE	PARENCHYMAL INFILTRATION	PER CENT OF SUSPECTS	PER CENT POSITIVE	PER CENT SUSPECT AND POSITIVE
White	M	76	67	2	7	3	1	2	1	2.6	9.2	11.8
	F	79	69	1	9	3	2	3	1	1.3	11.4	12.7
Japanese	M	12	10	0	2	0	0	1	1	0	16.6	16.6
	F	11	8	0	3	2	1	0	0	0	27.3	27.3
Chinese	M	9	6	0	3	1	0	1	1	0	33.3	33.3
	F	2	1	0	1	0	0	0	1	0	50.0	50.0
Total	M	97	83	2	12	4	1	4	3	2.1	12.4	14.4
	F	92	78	1	13	5	3	3	2	1.1	14.1	15.2
Total White		155	136	3	16	6	3	5	2	1.9	10.3	12.3
Total Japanese		23	18	0	5	2	1	1	1	0	21.7	21.7
Total Chinese		11	7	0	4	1	0	1	2	0	36.4	36.4
Total		189	161	3	25	9	4	7	5	1.6	13.2	14.8

It will be seen in table 5 that the percentage of positive X-ray plates is greater in both Oriental races than in white children; and that in Chinese children the percentage of positive plates was almost twice the percentage in Japanese and three and one-half times the percentage in white children. As noted before, the Chinese group is small and the results, therefore, may not give the true incidence in the race.

A slightly greater percentage of girls than boys of the white race had positive X-ray findings. If we consider the suspects with the positives this difference becomes less than 1 per cent. The number examined in both Chinese and Japanese is small, but the findings indicate a more frequent occurrence of demonstrable lesions in girls than in boys. The incidence of positive X-rays and positive skin tests for the whole group of 1,001 is 2.49 per cent. Johnson and Chadwick (7) report an incidence

of positive plates of 31 per cent for those reacting to tuberculin, and of 4.4 per cent for the whole group in children 0–17 years of age.

TABLE 6

The X-ray findings according to the amount of tuberculin producing a positive reaction

		0.1 cc. 1–1,000 dilution o.t.								0.1 cc. 1–100 dilution o.t.							
	Sex	Number	Negative	Suspects	Positive	Tracheobronchial	Pulmonary nodule	Tracheobronchial pulmonary nodule	Parenchymal infiltration	Number	Negative	Suspects	Positive	Tracheobronchial	Pulmonary nodule	Tracheobronchial pulmonary nodule	Parenchymal infiltration
White	M	16	10	0	6	3	1	2	0	60	57	2	1	0	0	0	1
	F	15	9	0	6	1	1	3	1	64	60	1	3	2	1	0	0
Japanese	M	7	5	0	2	0	0	1	1	5	5	0	0	0	0	0	0
	F	7	5	0	2	1	1	0	0	4	3	0	1	1	0	0	0
Chinese	M	5	2	0	3	1	0	1	1	4	4	0	0	0	0	0	0
	F	1	0	0	1	0	0	0	1	1	1	0	0	0	0	0	0
Total	M	28	17	0	11	% pos. 39.28				69	66	2	1	% pos. 1.44			
	F	23	14	0	9	% pos. 39.13				69	64	1	4	% pos. 5.78			
Total		51	31	0	20	% pos. 39.21				138	130	3	5	% pos. 3.62			

It will be seen in table 6 that the percentage of demonstrable lesions in the chest occurs ten times as frequently in those sensitive to 1–1,000 dilution as compared to those sensitive to 1–100 dilution. No difference occurs in the two sexes in those who reacted to 1–1,000 dilution. Slightly more girls than boys among those who reacted to 1–100 dilution had X-ray demonstrable lesions. Hetherington, *et al.* (6) say that "tuberculous lesions occur with much greater frequency among children who react to the smaller quantity of tuberculin than among those who do not react or react only to the larger quantity."

Table 7 shows that the percentage of demonstrable lesions among positive reactors increases with the degree of the skin reaction, being 4.54 per cent of those with one-plus reactions, 17.14 per cent of those with two-plus reactions and 31.81 per cent of those with three-plus reactions.

Dickey (12) found a relationship between large reactions and increased markings in the X-ray plates but not to other X-ray findings.

TABLE 7

The X-ray findings according to the size of the tuberculin reaction

	SEX	NUMBER	NEGATIVE	SUSPECTS	POSITIVE	TRACHEOBRONCHIAL	PULMONARY NODULE	TRACHEOBRONCHIAL PULMONARY NODULE	PARENCHYMAL INFILTRATION	TOTAL Number	TOTAL Negative	TOTAL Suspects	TOTAL Positive	TOTAL Per cent suspects	TOTAL Per cent positive
+	M	55	51	1	3	1	0	1	1	110	103	2	5	1.8	4.5
	F	55	52	1	2	1	1	0	0						
++	M	19	16	1	2	2	0	0	0	35	28	1	6	2.9	17.1
	F	16	12	0	4	1	1	1	0						
+++	M	23*	16	0	7	1	1	3	2	44	30	0	14	0	31.8
	F	21	14	0	7	2	1	2	2						
Total										189	161	3	25	1.6	13.2

* Includes one ++++ reactor with positive X-ray.

TABLE 8

The relationship of weight to X-ray demonstrable lesions

	POSITIVE X-RAY		NEGATIVE X-RAY	
	Number	Per cent	Number	Per cent
10 per cent or more under standard weight	4	16	109	11.7
9 per cent or less over or under standard weight	18	72	754	80.9
10 per cent or more over standard weight	3	12	69	7.4
Total	25	100	932	100

TABLE 9

The influence of density of population on the incidence of positive tuberculin reactions and on the incidence of positive X-rays

DISTRICT	NUMBER OF SCHOOLS	NUMBER OF CHILDREN EXAMINED	NUMBER POSITIVE TO TUBERCULIN	PER CENT POSITIVE	NUMBER POSITIVE X-RAYS	PER CENT POSITIVE X-RAYS
1	6	186	43	23.11	11	5.91
2	18	308	71	23.05	7	2.24
3	10	189	35	18.51	4	2.11
4	5	129	21	16.27	1	0.77
5	14	187	31	16.40	2	1.05
Total	53	1,001	201	20.08	25	2.49

Barclay (15) found "definite underweight did not occur more frequently in those with evidence of tuberculosis than in the nontuberculous." Table 8 shows that overweight and underweight children occurred more frequently among those with positive X-rays than among others.

Schools from districts of approximately the same density of population were grouped together. It should be pointed out that the schools in the first district contained the majority of the Japanese and the Chinese children considered in this study. The districts are arranged in order of decreasing density of population. It would appear that crowding plays a part in determining the incidence of infection and has an appreciable effect in increasing the number of lesions demonstrable by X-ray of the chest. Chadwick and Zacks (16) found that "different sections in the same city may show a wide variation in the percentage of infection" and "Congested areas show a higher percentage of infection."

SUMMARY

1. The incidence of positive tuberculin reactions in 1,143 children entering primary public-schools was found to be 19.86 per cent.

2. For 1,001 six-year-old children the incidence of positive reactors was 20.08 per cent; for girls, 20.70 per cent; and for boys, 19.49 per cent.

3. The incidence of infection among 29 Chinese children was 37.93 per cent; among 110 Japanese 21.81 per cent; and among 857 white children, 19.13 per cent.

4. The majority of positive reactors were not sensitive to 0.1 cc. of 1–1,000 dilution of O. T. Of those who reacted to the initial injection of tuberculin almost two-thirds had 3-plus reactions. Over two-thirds of those reacting only to the larger amount of tuberculin had 1-plus reactions.

5. Variations in percentages of standard weight were not reflected in the percentages of children having positive reactions.

6. The incidence of infection increased with increasing density of population.

7. Demonstrable tuberculous lesions were found in the X-ray plates of 13.22 per cent of positive reactors, which was equivalent to 2.49 per cent of the whole group. Positive X-rays were found in 10.32 per cent of white, 21.73 per cent of Japanese and 36.36 per cent of Chinese children who reacted to tuberculin. The Japanese and Chinese groups were small in number. More girls than boys had positive plates.

8. Of 51 children sensitive to 0.1 cc. of 1–1,000 dilution of tuberculin, 20, or 39.21 per cent, had positive X-ray plates. Of 138 children positive to 0.1 cc. of 1–100 dilution, 5, or 3.62 per cent, had positive plates.

9. The incidence of tuberculous lesion demonstrable by X-ray was seven times as great for those with 3-plus reactions as for those with 1-plus reactions.

10. Underweight and overweight children were found more frequently among those whose X-ray plates showed definite lesions than among those whose chest-plates were negative.

11. The percentage of positive X-ray plates was higher among children from congested districts than among others.

PART 2

The Sources of Tuberculous Infection in Children Entering Primary Schools

The following is a preliminary report on a suggested new approach to case-finding.

In an urban community the opportunities for infection of young children with the tubercle bacillus are many. We must consider, as possibilities, an infectious milk-supply, casual contact with many people and intimate contact in their own home.

Regarding the possibility of a contaminated milk-supply as being responsible for a large proportion of infection in young children, the following facts are important:

Eighty-nine per cent of the milk sold in the City is pasteurized. Only grade-A milk can be sold in the raw state. In 1926 a general test of the cattle in the area supplying milk to the City revealed 7.8 per cent as positive reactors. Two retests within the same year showed 3.9 and 1.0 per cent infected cattle. The percentages of positive reactors in general retests in 1927 and 1933 were 1.1 and 0.6, respectively. Harrington and Myers (3) conclude that the ingestion of dead tubercle bacilli in pasteurized milk could not account for a large percentage of positive reactors to tuberculin tests in children.

In tracing the sources of infection it is obviously impossible to deal with casual contacts. These children have not been at school a sufficient length of time to have the number infected appreciably changed by contact with other pupils and with teachers.

Intimate association with tuberculous individuals increases the incidence of positive reactors. It was considered that school-children of

the primary class have had their intimate contacts more or less limited to their own household. For this reason examination of the other members of the home should reveal the source of infection for a large proportion of those children reacting to tuberculin.

Slater and Jordan (17) suggested that

> with the percentage of reactors being as small as it generally is, it would not be an insurmountable task to make a study of the home contacts for the purpose of discovering the source of infection, and as a result many adults would be discovered with tuberculosis in the early stages.

Public-health nurses visited the homes of the child reactors to persuade the contacts to be examined. References from the family physician were required before the children were admitted to the clinic. Throughout the survey, the coöperation of family physician, school medical staff and clinic staff has facilitated the work. The procedure has been to examine and X-ray those who react to tuberculin.

Seventy-two families have been investigated to date; a total of 144 adults (62 male and 82 female), and 142 children (80 male and 62 female) were considered. Of the 72 families, 10 were Japanese, 11 Chinese and 51 whites. The source of infection has been definitely traced in 21 families. The primary case was discovered 18 times in 51 families, in which all adult members were examined. In the remaining 21 families, in which one or more adult members, residing at home, were not examined, tuberculosis in an adult was found only three times. A history of tuberculosis in intimates of 6 additional homes was obtained but not verified.

Larsen and Kalberg (18) in Denmark investigated the sources of infection for positive reactors among public-school children. They were successful in about 25 per cent of the cases. They worked with children of all ages in public-schools. It seems likely that the increased number of contacts in the schools and elsewhere outside the homes of the older children would decrease the probability of finding the sources of infection.

Of the 21 tuberculous individuals considered to be responsible for the infection of 21 primary-class children, 13 were previously known and on record at the Clinic. Eight new cases of tuberculosis were discovered through this survey. All the new cases were classified as minimal, 2 as apparently healed, and 6 as active. Seven were adults, and one a boy of fifteen years, with the so-called adolescent type of

disease. Of 14 tuberculous individuals previously diagnosed, 13 were adults and one a girl of fifteen with adolescent pulmonary tuberculosis. Four have died of tuberculosis: two are far advanced, three moderately advanced, and five minimal, apparently healed, or arrested. Both the father and mother were tuberculous in one family: the father giving the longer history of illness is considered to be the primary case in the family and probably responsible for infection of the school child. The original case was the father in 8 families, the mother in 8 families, a brother in one, a sister in one, other relatives in three families, and a lodger in one.

For a tuberculous person to be the source of infection presupposes that he has had positive sputum at some time. Hence, we should not expect to find the majority of subjects traced through this method to have minimal lesions. To date, all the new cases discovered through this survey have had minimal disease. Only five of 14 previously diagnosed tuberculous persons had minimal lesions. It would appear that, by investigating the home-contacts of infected children, we find a number of them tuberculous before their health is sufficiently impaired to bring them under observation. They are beyond the reach of the existing case-finding procedures.

The 7 adults with tuberculosis were found during the examination of 111 members of 59 families, an incidence of 6.30 per cent. The incidence of tuberculosis among 126 adults examined at the clinic recently was 15 per cent. This includes those examined as contacts, and those examined because of suspicious signs or symptoms.

Barclay (15), in a study of tuberculosis contacts in families, found demonstrable tuberculosis in 21.8 per cent of all contacts. He gives the incidence of tuberculosis in suspects examined at a sanatorium as 20 per cent.

Table 10 gives the findings in the 141 children (exclusive of the school beginners) of the 72 families studied to date. The ages range from nine months to nineteen years, with the average age of the group 8.31 years. The ratio of infection was 66.97 per cent. Tuberculous lesions were found in 18 children, or 12.76 per cent, of the whole group. Sixteen had positive X-ray plates and an additional three had suspicious markings. Two Chinese girls had tuberculosis of the cervical lymph nodes, and one of these was a suspect as well. Barclay (15), in a group of contacts whose average age was 10.1 years, found the incidence of tuberculosis to be 23.3 per cent. Johnson and Chadwick (7) give the inci-

dence of positive X-ray findings in children 0–17 years as 4.4 per cent.

It will be seen that there is a marked difference in the incidence of infection and of demonstrable disease in the racial groups. Infection was found in 54.16 per cent of white, 83.33 per cent of Japanese and 81.39 per cent of Chinese children; demonstrable tuberculosis (including extrapulmonary) occurred in 4.11 per cent of white, 13.04 per cent of Japanese and 26.66 per cent of Chinese children. Certain differences in the findings in boys and girls occurred in the racial groups. The incidence of infection in boys was higher than in girls of the white race,

TABLE 10

	SEX	NUMBER	NUMBER OF TUBERCULIN TESTS	NUMBER OF POSITIVE TUBERCULIN TESTS	PER CENT POSITIVE	NUMBER OF X-RAYS	NUMBER OF SUSPECTS	NUMBER OF POSITIVE X-RAYS	PER CENT POSITIVE	CERVICAL LYMPH NODES TUBERCULOUS	TOTAL TUBERCULOUS	PER CENT TUBERCULOUS
White	M	39	39	23	59.0	26	0	1	2.6	0	1	2.6
	F	34	33	16	48.4	21	1	2	5.9	0	2	5.9
Japanese	M	17	14	11	78.6	14	0	3	17.6	0	3	17.6
	F	6	4	4	100	6	0	0	0	0	0	0
Chinese	M	24	22	16	72.7	20	0	6	25.0	0	6	25.0
	F	21	21	19	90.5	19	2	4	19.0	2	6	28.6
Total		141*	133	89	67.0	106	3	16	11.3	2	18	12.8

* The total does not include one Chinese girl of 15 years who died of the adolescent type of pulmonary tuberculosis and who is considered to be the primary source in her family.

while among the Orientals more girls were infected. In the total group, 66.66 per cent of the boys and 67.24 per cent of the girls had positive skin-tests. More girls than boys had definite tuberculous lesions, namely, 13.11 as compared with 12.50 per cent.

Of the 16 positive X-ray plates, 5 showed tuberculosis of the tracheobronchial lymph nodes, two pulmonary nodules, three tracheobronchial tuberculosis with pulmonary nodules, one infiltration of the parenchyma, one miliary tuberculosis, one adolescent tuberculosis, and three pleurisy.

Table 11 shows a marked difference between the percentage of families, in the three races, White, Chinese and Japanese, in which a source of infection was found.

Regarding these findings, it is pertinent to point out that the mortality rate for tuberculosis is much higher in Orientals than in the white races. The ratio is approximately five to one. The rates for Japanese and Chinese are practically the same. We would therefore expect to be able to trace the sources of infection more frequently in Oriental than among white children. Other conditions being equal, there seems no reason why the source of infection should be found more frequently for Chinese than for Japanese children. The Japanese are much more cooperative than the Chinese in health matters, and, although living

TABLE 11

The bearing of race on the discovery of the primary case

	NUMBER OF FAMILIES	NUMBER IN WHICH SOURCE WAS FOUND	PER CENT OF SOURCES FOUND
White:			
Complete*	39	9	23.07
Incomplete	16	2	12.50
Japanese:			
Complete	8	3	37.50
Incomplete	2	0	0
Chinese:			
Complete	8	6	75.00
Incomplete	3	1	33.33
Total:			
Complete	51	18	35.29
Incomplete	21	3	14.29
Total	72	21	29.16

* Complete, refers to a family wherein all adult members residing in the home have been examined.

conditions for the two races are very similar, a greater dissemination of infection possibly occurs among the Chinese through ignorance, indifference and carelessness. But the incidence of infection in the children of the two races in table 10 is practically the same. It is difficult to see how this can explain the more frequent finding of the source of infection of Chinese children.

There are on record at this Clinic approximately 8 tuberculous individuals in the white population for each death from tuberculosis, 5 among the Japanese for each national who died of tuberculosis, and 3.6 in the Chinese population for each who died of tuberculosis during

1934. This would explain the finding of new cases of tuberculosis more frequently in the Chinese than in the Japanese, and more frequently in the Japanese than in the white population, but it should have no bearing on the percentage of infections traced for children of each race.

Certain observations in the school-beginners are of interest in connection with the discovery of the source of infection. Tables 12 and 13 would indicate that the result of the tuberculin test in the school-child

TABLE 12

The relationship of positive X-ray plates in children to the finding of the primary case

	NUMBER	SOURCE FOUND	PER CENT
Positive X-ray	16	6	37.50
Negative X-ray	56	15	26.78

TABLE 13

The relationship of the tuberculin reaction to the source of infection

(*a*) *The bearing of the amount of tuberculin to which a child is sensitive on the discovery of the source of infection*

	NUMBER	SOURCE FOUND	PER CENT
Positive to 1–1,000 dilution	29	14	48.27
Positive to 1–100 dilution	43	7	16.27

(*b*) *The size of the tuberculin reaction in the school child and its bearing on discovering the source of infection*

	NUMBER	SOURCE FOUND	PER CENT
+	34	6	17.64
++	15	1	6.66
+++	22	13	59.09
++++	1	1	100

gives a better clue in tracing the primary case than does the X-ray of positive reactors.

In other words, the character of the skin reaction is a better index of the intimacy of contact than is the presence of a definite lesion in the X-ray.

It will be seen from table 12 that the source of infection was demonstrated in a higher percentage of families where the school-child had definite X-ray findings than in those families in which the child had a negative plate, the tuberculin test being positive in both cases. But in

any application of this method in case-finding, 15 out of 21 adults with tuberculosis would be overlooked by omitting the investigation of the second group of families.

A higher percentage of infections is explained for those sensitive to the smaller amount of tuberculin than for those sensitive only to the repeat dose.

Table 13 (b) shows that the percentage of families in which the infection of the school-child is explained rises with increasing size of the skin reaction in the child. This would indicate that intimacy of contact with tuberculous subjects influences sensitiveness to tuberculin. The source of infection was found for 60.87 per cent of those children with 3- and 4-plus reactions, and for only 14.28 per cent for those with 1- and 2-plus reactions. Moreover, two-thirds of the 21 sources found were in families in which the six-year-old child had a 3- or 4-plus skin reaction. Dickey (12) found that contact children had larger skin reactions than positive reactors with no history of contact. His findings are in keeping with those in table 13.

SUMMARY

1. The report deals with the investigation of 72 families, 51 complete and 21 incomplete.

2. A source of infection was found in 21 families.

3. Of 21 primary cases 19 were adults and two were children of 15 years with adolescent type of disease.

4. Thirteen primary cases were previously known to be tuberculous.

5. Seven new primary cases were diagnosed among 111 adults, while one new primary case was diagnosed among 141 children.

6. All the newly discovered primary cases were minimal, 6 being active and 2 apparently healed.

7. Sixteen of 141 children had lesions in the chest demonstrable by X-ray. In addition, two had cervical lymphadenitis, and three were suspects.

8. Of 133 children, who reported the result of the tuberculin test, 89, or 66.97 per cent, had positive reactions.

9. The sensitiveness to tuberculin in the child, both as regards the size of the reaction and the amount of tuberculin required to produce it, shows a distinct relationship to the percentage of primary cases found.

10. A higher percentage of primary cases is found for children who

have demonstrable lesions than for those who have not, but the majority of primary cases are not traceable from this "lead."

11. Racial differences are marked. A higher percentage of primary cases is found for Orientals than for Whites. The mortality rates for each race has a bearing on this.

CONCLUSIONS

1. By tracing back into the families of young children infected with tubercle bacilli, it is possible to discover a fairly large number of tuberculous adults before these are discovered by other methods of case finding.

2. The majority of new cases, and the highest percentage for the number of individuals examined, will be found by examining the contacts of children sensitive to small amounts of tuberculin or of those children who have marked reactions.

3. In any event, the percentage of new cases found will be much smaller than is found among "contacts" and "suspects."

4. The presence of demonstrable tuberculous lesions in the children is not as useful a guide in case-finding as is sensitiveness to tuberculin, since the percentage yield is not so great and the majority of contact sources would be overlooked.

5. It would be interesting to determine the reliability of tuberculous lesions in older children as a guide in tracing infection.

6. The older children in the family should not be overlooked as possible primary cases within the family.

7. The incidence of tuberculosis among the children (other than those of the primary class) in these families is higher than the average in the childhood population, although not so high as among contacts of known tuberculosis.

8. Search for a primary case in the families where young children react to tuberculin is a feasible method of tuberculosis case-finding. Further investigation in other centres may show this method to be of practical value to school and municipal health-units.

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CONTACT AS A FACTOR IN THE TRANSMISSION OF TUBERCULOSIS

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This study was undertaken to determine the relative importance of different types of exposure in the dissemination of tuberculosis with a view to its control. The subjects of this survey were patients in the Tremont Tuberculosis Clinic[2] for the years 1933 and 1934. The purpose of the clinic is essentially to supervise tuberculous patients and their contacts. In addition to patients admitted voluntarily, various nursing and social bureaus refer patients to the clinic for examination. The complaints of these patients are usually loss of weight, cough, weakness, haemoptysis and other related symptoms. The district allotted to this clinic comprises a population of about 300,000, which is one-twentieth of the entire city population. The community includes a large indigent group, many of whom are supported by the Home Relief Bureau or other charitable agencies. Moreover, this group is typically representative of an urban populace, except for the absence of Asiatics.

Even before the tubercle bacillus was demonstrated by Koch, Villemin showed that tuberculosis was an infectious disease. Yet for a time this brilliant contribution to experimental medicine was lost in a maze of theory, the most important of which was the hereditary concept. The failure of the medical profession to recognize the infectiousness of the disease is not altogether beyond the pale of reason. It is impossible to elicit signs in many cases of tuberculosis. But, more important than this, is the fact that the disease is insidious and may be present for months and even years without any symptoms whatever, or these may be so trivial as to escape the notice of both patient and physician. In fact, the disease is very often discovered accidentally in routine examinations, or in the examinations performed while treating other conditions. The prolonged period in which the host harbors the disease totally unaware of its presence makes tuberculosis a social problem of great import.

Osler (1) felt that for the propagation of tuberculosis there were three

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essentials; the seed, the soil and the proper conditions for growth. From autopsy studies we conclude that most adults have healed tuberculous lesions. Our only problem is to determine what are the proper conditions for growth. In a study of the epidemiology of tuberculosis, it appears that there is a definite trend toward making the tubercle bacillus, *per se*, the "prime mover." In this presentation an attempt will be made to show that the "proper conditions" arose in those individuals who were exposed to positive-sputum cases. Repeated bombardment of tuberculous organisms on the body may so alter the "receptivity" as to finally result in propagation of the disease. Jessel (2) found that "in 1035 cases with positive sputum there developed in a period of 3.5 years 153 new cases among their contacts." Because of its widespread dissemination the "seed" was present in these new cases, the "soil" was unchanged, and it only remained to decide what factor or factors determined "the proper conditions for growth." The introduction of positive-sputum cases resulted in repeated bombardment of the contacts with tubercle bacilli, and this finally resulted in the proper conditions for growth.

No clinical study of pulmonary tuberculosis is of value without the use of the X-ray. This modality, as we know, has revolutionized chest diagnosis to a remarkable degree. It has served to demonstrate tuberculous lesions when all other diagnostic measures have failed. Moreover, it has been the medium for showing that the "phthisical habitus" and "pretuberculous" patient already harbor the disease the physical signs of which are not manifest. Fishberg (3) concluded that the incidence of tuberculosis in individuals married to tuberculous mates was not increased. With the more extensive use of X-rays, considerable doubt has been cast on this opinion. Fishberg's citation of the husband whose three wives succumbed to the disease is interesting in the light of our present knowledge as gained by the X-ray. While he regards the husband as "father immunity," it seems that this is a case of well-defined tuberculous cavity or tuberculous lymph node emptying into the trachea or bronchus. It is not uncommon to demonstrate cavities by X-ray which are not detected by physical examination.

Only those patients who attended the clinic are included in the survey. Although, in not a few instances, several members of a family were known to have tuberculosis, nevertheless, they were not considered except as a source of contact. Moreover, if two members of a family were afflicted and there was no other source of contact, only one was

considered in contact with tuberculosis and the other was regarded as the primary case.

It was often necessary to judge which of two or more cases preceded the others in time of occurrence. This was decided as often as possible by the history in the respective cases. The intimacy of contact was not considered. If one member of a family had a positive sputum, the other members were listed as contacts to positive sputum, except where tuberculosis was definitely present before the onset of the positive-sputum case. As regards children, if a relative was a definite case of tuberculosis but died before the birth of the child and there were no other living known contacts, the child was considered as having no contacts. A few of the deceased cases were known to have had positive sputum, but their contacts were listed as exposed to deceased tuberculous patients.

TABLE 1

Number and per cent of individuals examined

	NUMBER OF INDIVIDUALS			PER CENT	
	Total	Adults	Children	Adults	Children
Individuals examined	3,057	1,802	1,255		
Diagnosed cases of tuberculosis	777	730	47		
Number of diagnosed cases of tuberculosis in contact to tuberculosis cases	298	260	38	33.5	80.9

In all, 3,057 individuals were examined. The adults numbered 1,802 and the children 1,255. There were 777 definite cases of tuberculosis: 730 adults and 47 children. The small number of definite cases in children (47) is striking as compared to the relatively large number in adults (730). Wood (4) stated that "if too much attention is paid to child contacts, attention may be withdrawn from the far more important group, namely, the adolescent and young adult contacts." While we may safely say that too much attention cannot be paid to any contacts, the small number of cases in the child-group is surprising.

Of 730 cases of tuberculosis in adults, 260 (33.5 per cent) were in contact with known tuberculous patients. In contrast, 38 (80.9 per cent) of the 47 cases of tuberculosis in children were in contact with known tuberculous patients. It is difficult to trace the contacts of adults. They move in a wide circle of friends and associates. In the case of a child the family circle comprises almost the entire extent of

his contacts. This, in a measure, explains the high incidence of contact to tuberculosis in tuberculous children.

Fishberg (5) states that tuberculosis is more a problem of predisposition than of infection. But, as shown in table 2, of 205 individuals exposed to positive sputum, 49 (23.9 per cent) contracted the disease, while, in 115 contacts exposed to tuberculous patients with negative sputum, only 15 (13.0 per cent) contracted the disease. Can it be stated in all fairness that those patients in contact to positive sputum cases showed a "predisposition?" It would seem much more logical to assume that the repeated doses of organisms were responsible for the advent of the disease. This was also observed in Jessel's cases (2).

Of 305 contacts exposed to tuberculous patients now deceased, 112 (36.7 per cent) contracted the disease. This larger percentage (36.7),

TABLE 2

Incidence of tuberculous disease in adult contacts according to types of exposure

TYPES OF EXPOSURE	CONTACTS DIAGNOSED			PER CENT	
	Total	Tuberculous	Nontuberculous	Tuberculous	Nontuberculous
Positive sputum	205	49	156	23.9	76.1
Deceased cases of tuberculosis	305	112	193	36.7	63.3
Sputum unknown	486	84	402	17.3	82.7
Sputum negative	115	15	100	13.0	87.0
No known tuberculosis	691	470	221	68.0	32.0
Total	1,802	730	1,072	40.5	59.5

as compared to that of occurrence in the positive-sputum contacts (23.9) is readily understood. Patients who died of the disease were for some time bed-ridden, and required constant and intimate attention. This afforded even greater opportunity for close contact than with the usual positive-sputum case. It may be stated here that a case of tuberculosis showing a definite cavity by X-ray was placed in the positive-sputum group, regardless of the sputum report. From our hospital experience we have found that repeated sputum examinations almost invariably reveal positive sputum in cases of cavity formation.

Unfortunately, a large number of the original cases of tuberculosis were not patients in our clinic. We were unable to learn their sputum reports and therefore we have listed them under "unknown sputum." There were 486 patients exposed to unknown sputum cases. Of these,

84 (17.3 per cent) contracted the disease. This percentage is almost an arithmetical mean between the percentage of tuberculous patients exposed to positive sputum and the percentage of tuberculous patients exposed to negative sputum.

That some people enjoy a relative immunity to tuberculosis we cannot gainsay. But the immunity is relative and not absolute. In family A, the father was found to have a productive apical lesion; the daughter was entirely negative; the son, who was confined to a sanatorium, had an extensive caseous tuberculosis with large cavities. The son returned home. The father and daughter were again examined after two months of exposure to the boy. The father now showed a moderately extensive pneumonic tuberculosis with beginning caseation while the daughter showed a widespread exudative lesion. (The terminology used here has been adopted from the classification by Ornstein, Ulmar and Dittler (6).) Had not the son returned home it would appear that the daughter had been spared from tuberculosis by virtue of her immunity to the disease.

It is difficult to understand why one particular member of a family contracts the disease and not the others. It may be that this afflicted individual is at home or about during the period of positive sputum in the original case, or it may be that a greater intimacy is established between this member and the original case. But very often no reason is apparent. Thus in family V of 7 children, the father is a case, as are one son and one daughter. According to the history obtained, the father did not sleep with either child nor did the tuberculous children sleep together. Von Behring (7) felt that tuberculosis was ordained in childhood but often required years before it became a clinical entity. Many cases may be explained on this basis. The parental cares and intimacies toward infants and very young children may be responsible for the development of tuberculosis in later life. The organisms from the tuberculous parent may be "stored" in the lymphatic system of the child.

In this paper, children were considered, first, as regards tuberculous disease, and secondly, as regards tuberculous infection. Tables 3 and 4 give statistics for infants and children up to sixteen years of age, comprising the preschool and the school group. At school-age the opportunities for contact are the same in all children. Therefore, the general conclusions to be deduced for the preschool group are not altered by school contacts except arithmetically. Because of the limited sources

of contagion outside of the immediate family circle, tables 3 and 4 are the more valuable from which to draw conclusions.

The intracutaneous (Mantoux) test was performed on all but 45 of the children. This was done in the usual manner, 0.1 mgm. of O. T. being injected intracutaneously into the forearm. The tests were read

TABLE 3

Incidence of tuberculous disease in 1,210 child contacts and their response to tuberculin, according to the type of exposure

(45 individuals of 1,255 were not tuberculin-tested)

TYPE OF EXPOSURE	INDIVIDUALS				PER CENT		
	Examinations	Diagnosed tuberculous	Mantoux		Diagnosed tuberculous	Mantoux	
			Positive	Negative		Positive	Negative
Positive sputum	212	16	139	73	7.5	65.6	34.4
Deceased cases of tuberculosis	220	2	156	64	1.0	70.9	29.1
Unknown sputum	417	19	250	167	4.6	60.0	40.0
Negative sputum	197	1	55	142	0.5	27.9	72.1
No known tuberculosis	164	9	66	98	5.5	40.2	59.8
Unclassified: no Mantoux performed	45						
Total	1,255	47	666	544			

TABLE 4

Degree of reaction to Mantoux test in child contacts on basis of types of exposure

TYPE OF EXPOSURE	NUMBER					PER CENT			
	Total	1+	2+	3+	4+	1+	2+	3+	4+
Positive sputum	139	23	73	26	17	16.6	52.5	18.7	12.2
Deceased, tuberculosis	156	26	96	29	5	16.7	61.5	18.6	3.2
Sputum unknown	250	62	136	48	4	24.8	54.4	19.2	1.6
Sputum negative	55	21	26	8	0	38.2	47.3	14.5	0
Unknown tuberculosis	66	20	36	7	3	30.3	54.6	10.6	4.5
Total	666	152	367	118	29	22.8	55.1	17.7	4.4

in 48 hours. In positive reactions depending upon the size of the wheal and swelling of the arm, the readings were interpreted as Mantoux 1+, 2+, 3+, or 4+. The Mantoux 1+ consisted of a wheal about 1 cm. in diameter, while in the 4+-cases practically the entire forearm was red and swollen and had a necrotic centre.

There were, in all, 47 definite cases of tuberculosis in the infants and

childhood group. The diagnosis was made by history and X-ray. No attempt was made to differentiate between so-called childhood tuberculosis and the adult type. Most of the cases showed parenchymal involvement. A few had only large paratracheal or mediastinal lymph nodes, but these were, clinically, cases of tuberculosis. Three cases were included that were Mantoux-negative. Two of these were Mantoux-tested three times, and each time the reading was negative. Both children were in contact with positive-sputum cases, and one slept with her contact. The latter had a clinical course, symptoms and X-ray findings similar to the group described as "epituberculosis" by Eliasberg and Neuland (8), and Goldberg and Gasul (9). The other child, a colored girl age 2, had an immense mediastinal lymph node and definite parenchymal changes. It is interesting to note that this child had one sister, age 3, with a similar X-ray shadow, and another, age 4, with a definite parenchymal lesion. Each of the two sisters had a 2+ Mantoux reading.

TABLE 5

Analysis of the cases of tuberculosis in children

	REACTION					TOTAL
	Mantoux negative	Mantoux 1	Mantoux 2	Mantoux 3	Mantoux 4	
Number.....	3	7	28	5	4	47

The tuberculin reaction is accepted as conclusive evidence of tuberculous infection (10), but is the reverse true; that is, does a negative reaction mean absence of tuberculous infection? Desperately ill children often fail to give a Mantoux reaction. Austrian (11) has cited examples of negative tuberculin reactions in children known to have had a previous positive reaction. Workers (12) with *BCG* found positive reactions with tuberculin and, months later, negative reactions. But, according to our present standards, a positive Mantoux reaction is necessary to establish a diagnosis of tuberculosis in children. In view of this, the final diagnosis of tuberculosis in the three children with negative Mantoux readings is held in abeyance, although they have been included with the cases of tuberculous disease in children. It is hoped that some light will be thrown upon these obscure cases that go "begging" for a diagnosis.

Of 212 children exposed to positive sputum, 16 (7.1 per cent) con-

tracted the disease. Only 2 of 220 (1 per cent) children in contact with tuberculosis patients who died contracted the disease. This decrease is in sharp contrast to the rise in the adult group (table 2). The seeming inconsistency is explainable. Because of the fear of contagion for the child, and because the disturbances and antics of a child are intolerable to the very sick, it is uncommon to have children playing about the sick-room. As mentioned previously, adults establish very close association in dispensing care to the dying.

There were 9 cases that occurred in children who were not in contact with any known tuberculosis patients. Only one case was listed that was in contact with a negative-sputum case. The cases cited here are too few in number for study. Suffice it to say that very few cases of tuberculosis in children occur in contacts to negative sputum or nontuberculous patients.

One fact may be worthy of mention in connection with the paucity of cases (47) noted in the childhood group. Epituberculosis (8) (9) may entirely resolve without leaving any trace by X-ray. In a few of our cases we have been fortunate in demonstrating the lesion with its subsequent complete resolution. During the onset or early stage of the disease the symptoms often resemble a simple cold or grippe. Many mothers insist upon keeping the child confined when these symptoms are present. When the child finally appears at the clinic, a previously existing lesion of epituberculosis may have undergone complete resolution.

Schrempf (13) found that, of 7,214 school children, 1,460 (20.2 per cent) gave a positive tuberculin test. But in children exposed to tuberculosis in the family, 89.3 per cent were positive to the Mantoux test. He further states that, in children exposed to tuberculosis outside of the family, 56.9 per cent were Mantoux-positive. Only 29.9 per cent of children with weak bodily structure were Mantoux-positive. This was only slightly higher than that of school-children in general, and he therefore concluded that constitutional factors play no part in the development of the disease.

Of 212 infants and young children exposed to positive-sputum cases, 139 (65.6 per cent) had positive Mantoux reactions. In the children exposed to tuberculosis patients who died, 156 (70.9 per cent) of 220 had positive Mantoux reactions.

There was a total of 164 children in the group exposed to nontuberculous patients and 56 (36.4 per cent) had a positive Mantoux. Of

197 children exposed to negative-sputum cases of tuberculosis, 55 (27.9 per cent) were Mantoux positive. It appears from this that, as regards tuberculous infection, there is no greater hazard in exposure to negative-sputum cases than in exposure to nontuberculous cases. This is the same conclusion drawn in the case of tuberculous disease in children in similar groups.

In the children exposed to positive sputum cases, 17 developed a 4+ Mantoux reaction. No 4+ Mantoux reaction occurred in children exposed to negative-sputum cases, and only 3 were present in the children not exposed to known cases of tuberculosis. It has been suggested that the increased reaction to tuberculin in children exposed to positive-sputum cases is explained by the fact that these children are exposed at a very early age. But this does not appear to be sustained in those tuberculous children exposed at a very early age who have a 1+ or 2+ Mantoux readily. Perhaps the hypersensitiveness is due to the fact that the infection was very recent. This is consistent with the large number of 4+ Mantoux reactions occurring in contacts to positive-sputum cases. Certainly, in a few cases, hypersensitivity to tuberculin is as much a mystery as are the numerous cases of hypersensitivity noted in other allergic diseases.

The 2+ Mantoux reading is the most common in all the groups. The 4+ Mantoux reading is the least common in all the groups, including the one exposed to positive sputum. Even in the cases of tuberculosis in children, the number of 2+ Mantoux readings is overwhelming when compared to the other Mantoux reactions in this group.

SUMMARY

This study gives conclusive evidence that contact to positive sputum is the greatest single factor in the spread of the disease. One might take issue with the value of our conclusions as regards positive sputum on the ground that these individuals in contact with positive sputum cases are offspring of tuberculous parents and hence inherit the "tendency" to contract the disease. But this same "tendency" must be present in those individuals who are in contact to negative-sputum cases. In these we note a sharp drop in the incidence of disease.

Children exposed to positive-sputum cases show a high incidence to both tuberculous disease and tuberculous infection. Those exposed to negative-sputum cases have a low incidence to tuberculous disease and tuberculous infection. Here again, the "tendency" to acquire the

disease was the same in both groups. Although no figures were entered in the tables, many of the Mantoux negative children had grandparents or blood-relations afflicted or dead of the disease. In general, these children were never in contact with the primary cases.

The intensity of the Mantoux reaction in the individual case depends largely upon the time interval between the period of exposure to positive sputum and the date of the test. The more recent the exposure the greater is the reaction to tuberculin. It is not definite whether the time-interval dates from the period of the primary infection or from the period of exposure to positive sputum. While no time intervals were taken, this seems to be the most probable explanation for the relatively large number of 4+ Mantoux cases in the positive-sputum group (table 4).

CONCLUSIONS

1. Positive sputum is the greatest single factor in the spread of pulmonary tuberculosis.
2. The incidence of tuberculous infection in children depends largely on positive-sputum contact.
3. Pulmonary tuberculosis in infants and young children is not very common.
4. In this study contacts exposed to positive-sputum cases show an increased degree of sensitivity as is indicated by the intensity of reaction to tuberculin.
5. Control of positive sputum cases is the most effective means of limiting the spread of the disease.

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LATENT SOURCES OF CONTACT IN TUBERCULOSIS

BURT R. SHURLY AND D. S. BRACHMAN[1]

The National Tuberculosis Association through its local societies has helped materially in publicizing the slogans sponsoring early diagnosis. It has been made clear that beneficial results from an early diagnosis are (1) the patient is more frequently cured; (2) there is less opportunity to spread the infection to others; and (3) the lowered hospital cost results in great financial saving to the community.

For the last five years a concentrated educational campaign has been pressed locally among the physicians, other health-workers and the public. The campaign is a coöperative one between the Detroit Tuberculosis Sanatorium (the local Tuberculosis Association), the Wayne County Medical Society and the Detroit Department of Health. The work among the physicians included lectures, demonstrations, explanatory booklets and personal interviews. For the laymen there were frequent radio talks, newspaper articles and wholesale distribution of posters and leaflets, the latter going into practically every home through the schools. Patients were advised to go to their family physicians for examination as soon as symptoms appeared.

In spite of this comprehensive educational program the percentage of those diagnosed as minimal tuberculosis still remained low. It became apparent, therefore, that the great proportion of moderately advanced and far-advanced disease should be attacked in other ways.

Extensive work was carried out among the apparently healthy schoolchildren locally. First the younger children were examined and later the high-school students, using the tuberculin test and X-ray screening procedure. In the school year, 1934–1935, our work was limited to the 11th and 12th grades, where, in 6,733 tests completed, 34 cases of active adult type were found, or 0.5 per cent of those tested (ages 15 to 19 years). In another group of 605 apparently healthy food-handlers, mostly female, ages 18–25, we found 6 having active adult-type disease, or 1 per cent.

As a result of these findings, similar to those discovered in other parts

[1] Detroit, Michigan.

of the United States (1), we undertook to examine the local group of unemployed homeless men who were housed and fed in a large industrial building, loaned for that purpose. The result of this work in Fisher Lodge is very enlightening from many angles, particularly since tuberculosis is rightly considered to be in great part a socioeconomic disease. A portable X-ray machine was brought to the building, and the men were rayed in the order in which their names were filed. The enrollment of local unemployed in the Lodge was 960 but, as there were new admissions and discharges daily, we continued X-raying until a thousand were completed.

TABLE 1

Examination results of 1,000 unemployed homeless men (nonselected)

Tuberculosis:	
Active	21
Inactive	46
Old pleurisy	40
Cardiac:	
Endocardial	
Compensated	6
Decompensated	2
Hypertensive	2
Aneurysm	4
Carcinoma	2
Occupational fibrosis	7
Low-grade respiratory infection	8
Bronchiectasis, marked	1
Old empyema abscess	1
Observation	6

The tentative diagnoses procured from the examinations are shown in table 1. Since in this work we were primarily interested in tuberculosis, patients with other conditions were referred to general hospitals for further care, through the Lodge physician. Twenty-one cases of active tuberculosis were found and are classified according to age-groups and color (table 2); the 46 inactive cases are similarly classified in table 3.

It is interesting to note the nativity of the unemployed homeless men in comparison with the total resident in the community (table 4). In Detroit it is readily seen that the nativity groups are an important factor in antituberculosis educational planning. It was considered ad-

visable therefore to analyze further the active cases found according to this classification.

Unfortunately, a rumor was spread about in the Lodge that the X-ray work was a plan to discharge some of the men to make room for others. This sounded plausible to the inmates because some of them did not return, the active tuberculosis patients being transferred to hospitals. Thus, toward the end of the first 500 men completed, many

TABLE 2

Active tuberculosis in age-groups

	AGE-GROUP					TOTAL
	21–30	31–40	41–50	51–60	61–up	
White	94	273	393	100	14	874
Colored	22	65	32	7	0	126
Total examined	116	338	425	107	14	1,000
Number of cases found	1	11	8	0	1	21
Per cent of cases found	0.8	3.2	1.8	0.0	7.1	2.1

TABLE 3

Inactive tuberculosis in age-groups

	AGE-GROUP					TOTAL
	21–30	31–40	41–50	51–60	61–up	
White	94	273	393	100	14	874
Colored	22	65	32	7	0	126
Total examined	116	338	425	107	14	1,000
Number of cases found	3	14	21	8	0	46
Per cent of cases found	2.5	4.1	4.9	7.4	0	4.6

were excused because of "previously arranged interviews for work," probably several with suggestive symptoms. In the last groups examined, however, excuses were not accepted, and the diagnosed cases increased to similar proportions to the original group. This is shown in table 5, giving results in (a) per groups of 100 and (b) per groups of 200, in the order of examination.

It appears that the actual percentage of active cases present in the Fisher Lodge type of men would thus be between 2.1 per cent found in

TABLE 4

*Detroit's population by nativity, 1933**

	NUMBER OF RESIDENTS	EXAMINATIONS AT FISHER LODGE
Armenia	2,125	0
Austria-Hungary	16,167	12
Canada	88,996	2
Czechoslovakia	5,970	1
England and Wales	28,330	33
France	2,210	35
Germany	31,000	64
Greece	6,037	1
Ireland	9,285	112
Italy	27,000	16
Lithuania	4,625	27
Mexican	6,170	1
Netherlands and Belgium	10,472	7
Norway, Sweden and Denmark	7,420	17
Poland	62,297	146
Rumania	7,120	5
Russia	20,617	17
Scotland	22,249	29
U. S. Whites	992,310	289
U. S. Negroes	113,606	126
Yugoslavia	8,529	6
All others	10,739	54
Totals	1,483,274	1,000

* Based on percentage distribution in 1930 (Blakeslee).

TABLE 5

Active tuberculosis diagnosed in (A) groups of 100, (B) groups of 200

A	B
3	
4	7
2	
5	7
1	
1	2
0	
0	0
3	
2	5
21	21

the total 1,000, (table 6) and the 3.0 per cent in the first 500 (table 7). In comparing the findings in these two groups according to nativity one

TABLE 6

Active tuberculosis classified as to nativity
(Total found, 21 in 1,000, or 2.1 per cent)

	AMERICAN		POLISH	IRISH
	White	Colored		
Number examined	289	126	146	112
Number found tuberculous	4	3	4	2
Per cent found tuberculous	1.3	2.3	2.7	1.7

Note: One case of active tuberculosis was found in each of the following nativity, the number examined being shown in parenthesis: Bohemian (4), Finnish (6), French (35), German (64), Lithuanian (27), Filipino (2), Russian (17), Spanish (8).

TABLE 7

Active tuberculosis classified as to nativity (first 500)
(Total found, 15, or 3.0 per cent)

	AMERICAN		POLISH	IRISH
	White	Colored		
Number examined	135	81	71	50
Number found tuberculous	4	2	3	2
Per cent found tuberculous	2.9	2.3	4.2	4.0

Note: One case was found in each of the following nativity, the number examined being shown in parentheses: German (30), Lithuanian (13), Filipino (2), Spanish (4).

TABLE 8

Inactive tuberculosis classified as to nativity

	AMERICAN		POLISH	IRISH	GERMAN	LITHUANIAN
	White	Colored				
Number examined	289	126	146	112	64	27
Cases found	16	4	4	7	5	2
Per cent found	5.5	3.1	2.7	6.2	7.8	7.4

Note: One case of inactive tuberculosis was found in each of the following nativity, the number examined being shown in parenthesis: Austrian (4), English (33), Hungarian (8), Roumanian (5), Serbian (4), Slavish (4), Scotch (29).

immediately notices the marked disparity in figures that results from the inconclusively small numbers studied. Outstanding in both groups, however, is the fact that the Polish and Negro rate is above the average.

Similar results in this community were apparent among the senior high-school students and in approximately the same proportion.

One of the men among the inactive tuberculous (table 8) is an interesting example of tuberculosis not breaking down against all reason, judging from his history.

Case Y was admitted to a tuberculosis sanatorium with positive sputum 21 months ago and had a phrenicectomy. He spent 13 months as an inpatient,

TABLE 9

Active tuberculosis: stage of disease and history

CASE	AGE	COLOR	CLASSIFICATION	SYMPTOMS	SIGNS	CONTACT
1	48	W	IA	−	−	−
2	46	W	IIIB	+	+	−
3	31	W	IB	+	−	+
4	33	W	IIIB	+	+	−
5	34	W	IA	−	−	−
6	36	W	IIB	+	+	+
7	31	W	IA	−	−	−
8	43	C	IA	−	−	−
9	37	W	IA	−	−	−
10	36	C	IA	−	+	−
11	50	W	IIIA	−	+	−
12	21	W	IIIB	+	+	+
13	34	W	IIA	−	+	−
14	66	W	IB	+	+	+
15	44	W	IA	−	−	−
16	42	W	IA	−	−	−
17	46	W	IIA	−	+	−
18	33	W	IB	+	−	−
19	40	W	I	−	−	−
20	40	C	IIA	−	+	−
21	46	W	IA	−	−	−
Total				7	10	4

was aspirated 52 times, and developed empyema 8 months ago. He was discharged from hospital 5 months ago, when he accepted a job with a circus. During this period his life was very irregular, often without sleep. In addition the job called for frequent use of an 18-lb. sledge-hammer. His X-ray at our examination showed no apparent activity of his previous disease.

The active cases of tuberculosis classified as to degree of involvement, symptoms, abnormal physical signs and contact history are shown in table 9. Those having symptoms should have gone to the Lodge physi-

cian for examination, but in the majority of cases they "didn't think it necessary." Two of them, on the other hand, were aware they were tuberculous, though denying the history on admission, and knowingly exposed others to the disease, refusing sanatorium care originally.

One of the important differences between tuberculosis and such infections as measles, diphtheria, smallpox, etc., is that in tuberculosis symptoms may not appear for weeks and sometimes for several months after actual onset of the disease. In the Fisher Lodge work there were no symptoms in 14, or 66.6 per cent, of those examined. Abnormal physical signs were absent in 11, or 52.3 per cent. In 14 adult-type disease cases discovered in a local high-school in 1932 through a similar program (2) symptoms were absent in 11, or 78.5 per cent.

Another recognized difference in tuberculosis is that close and continuous or often repeated short contact is required. Since such exposure is most likely to occur in one's immediate family, on the discovery of a clinical case of tuberculosis, it is there that we first look for the source of the disease as well as for infected contacts.

The latest Detroit Department of Health monthly report (June, 1935), classified as to contact (3), shows that 38 per cent of the adults examined were known contacts, while 62 per cent had no known contact with tuberculosis. Twenty-one per cent of the known contacts were found to have tuberculosis, and 20 per cent of those who had no known contact. Thus, it is very apparent that examining contacts alone will result in missing a large number of patients. At Fisher Lodge a contact history was present in 19.4 per cent.

According to Dublin, previous sanatorium effectiveness depended on ability to serve minimal cases. He claimed that, in obtaining 40 per cent of cases in the incipient stage, a 10 per cent saving in mortality could be accomplished. "Even if sanatorium care were not made more effective," he said (4), "a change of the present proportions to 60 per cent incipient, 20 per cent moderately advanced and 20 per cent far advanced would increase the annual mortality saving from 10 per cent to 22 per cent per year." With recent advances in collapse therapy the above suggested proportions of involvement in the patients hospitalized would result in an even greater mortality saving.

Particularly interesting are the stages of disease in the Lodge group (table 10), compared with those discovered in our senior high-school program and those found by the usual means, the latter as reported by the Detroit Department of Health. It is apparent that, in order to

find a larger proportion of minimal cases, it is advisable to use the tuberculin-X-ray screening method more generally, irrespective of the presence or absence of symptoms, abnormal physical signs or contact history. The 6 cases of adult type found among food-handlers were divided into 2 minimal (33.3 per cent), 3 moderately advanced (50.0 per cent) and 1 far advanced (16.7 per cent), and were not included in the table because of the small number involved.

An analysis of the 14 adult-type cases discovered in a local high-school in 1932, pointed very definitely to a girl with an active moderately advanced tuberculosis spreading the disease to five of her classmates. This girl had no symptoms, and was active in the basket-ball and hockey

TABLE 10

Stages of disease as diagnosed by: A and B, case-finding unit: C, usual means

	MINIMAL	MODERATELY ADVANCED	ADVANCED	TOTAL CASES
	per cent	*per cent*	*per cent*	
A				
Senior high-school				
Ages 14 to 19.....	82.4 (28)	17.6 (6)	0	34
B				
Fisher Lodge				
Ages 21 upwards.....	52.4 (11)	23.8 (5)	23.8 (5)	21
C				
Usual means				
Ages 16 upwards.....	19.1 (28)	36.7 (54)	44.2 (65)	147

teams at the time of diagnosis. Incidentally, her own source of contact was discovered a year later, when she learned that a man who had boarded in her home for two months died from tuberculosis.

This work at Fisher Lodge now completes the picture in that it shows how this spreading of tuberculosis occurs. The residents at the Fisher Lodge, on resuming employment, are discharged from there and often become boarders or lodgers. If they have active tuberculosis, knowingly or otherwise, the story of the above high-school student is repeated.

Pathologically, this student had moderately advanced disease, with definite abnormal physical signs, though she had no symptoms and this in spite of her activity on the school basket-ball and hockey teams.

She was an innocent source of contact to her classmates because of the absence of symptoms. This is further clarified by the interesting work of Long (5). He shows that "tubercle bacilli are commonly hundreds or thousands of times as numerous in the semi-liquid contents of softening caseous nodules as in the necrotic walls of old cavities." He further states that "softening of the tubercle is a specific pathological process and is distinct from caseation." It would appear therefore that some early lesions may cause more spread of the disease than other advanced conditions. The probability of latent sources of contact thus becomes greater.

Dorland's (6) definition of a carrier is "an individual who harbors in his body the specific organisms of a disease without manifest symptoms and thus acts as a carrier or distributor of the infection." Tuberculosis carriers may therefore be said to permeate most places in which people congregate, and especially where there is overcrowding. The disease may be spread in places of employment, education or recreation. In tuberculous households the danger is probably greater because of the frequency and size of the infecting dose.

In the Polish population, it is recognizable that a large proportion have a marked dislike for hospitalization, and this appears particularly when the disease is tuberculosis. There are apparently both social and psychological factors involved, the correction of which is quite a problem. A broad and comprehensive educational program is now being initiated and will be continuously pushed for several years. Coöperation in this movement has been promised by practically all groups in the area involved.

The mortality rate from tuberculosis in the colored is six times that of the whites. In the tuberculin-X-ray screening of the apparently healthy, however, our work shows they have but a slightly higher rate of disease than the general average. Since the colored in this community are very coöperative in accepting immediate hospitalization, their high mortality rate is likely due in great part to overcrowding. There is also the probability of overwhelming doses of infection. There is increasing doubt as to whether the so-called low immunity of the race exists. Pinner's observations on immunity are very pointed (7): "It is in no way permissible to ascribe all healing processes to specific immunity; constitutional factors, environmental influences, mechanical conditions in the local lesion; they and many factors decide the clinical course."

The Federal local slum-clearance plan includes an area populated by the colored people and, if properly managed, will eventually show an immense improvement on the tuberculosis rate, by removing the overcrowding. It is hoped that the Health Department will have an active part in the administration of the re-housing areas, as is the case in some European countries, so that hygienic and sanitary conditions will remain at the best. In some cities abroad a yearly lease is not renewable without the approval of the Health Department.

The findings among all poor socioeconomic groups, including white and colored, in the rural areas of our county are less than those among similar groups in Detroit. Perhaps, as far as tuberculosis is concerned, re-housing should be carried out, if possible, in the surrounding rural areas rather than concentrated in large city buildings. The work of Gorgos in the Panama Canal Zone, in handling pneumonia there, is much to the point. He discontinued quartering negroes in large barracks with marked improvement in the situation. Quoting Bushnell (8): "When men were later permitted to live in huts with their families and to prepare their own food, the result was worse ventilation and worse food but the diminished liability to infection more than counterbalanced these disadvantages."

SUMMARY

1. Tuberculosis may be active for weeks and sometimes for several months before producing recognizable symptoms.

2. Apparently healthy people unaware of having the disease may therefore act as tuberculosis carriers.

3. From the adolescent age onward such carriers are not infrequently found wherever people congregate in large numbers.

4. Tuberculosis is more likely to spread where people gather regularly, whether for work, education, recreation or food.

5. Some people knowingly having active disease become a latent source of contact in deliberately masking their symptoms by calling their condition "bronchitis," "bronchiectasis," "pulmonary abscess," etc.

RECOMMENDATIONS

1. Boarders or lodgers should not be accepted, particularly in homes where there are children, without first having an X-ray of the chest.

2. Teachers and other school-workers should be required to have an X-ray with or without a preceding tuberculin test.

3. High-school and college students should be required to go through tuberculin-test-X-ray screening before being accepted for athletic teams.

4. Modern case-finding methods should be required in all places where people gather regularly, whether for work, education, recreation or food.

5. Re-housing is strongly recommended in every so-called slum area. This is especially true in certain colored districts. Best results in tuberculosis are likely to be procured by transferring the re-housing to rural areas and single homes.

6. More education is advisable among some foreign-nativity groups along the lines of inducing them to take advantage of hospitalization.

7. Physicians may well carry out a tuberculin-X-ray case-finding program among the general population, especially from the adolescent ages upwards. This applies particularly to the poor sections of large cities where there is usually overcrowding. One might anticipate finding close to one per cent of these, that is approximately one in every hundred, with adult-type tuberculosis.

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THE EFFICACY OF TUBERCULOSIS CONTROL

A STATISTICAL ANALYSIS

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The City of Peoria, Illinois, a city in the 100,000 population class according to the 1930 Census, began the systematic control of tuberculosis in the year 1918 by opening the Municipal Tuberculosis Sanitarium with 20 beds. By the year 1928 the bed capacity of the Institution was gradually raised to 92 beds. A Chest Clinic for diagnosis and follow-up was also maintained since 1907.

Prior to the year 1930, however, the Sanitarium was prepared to give only domiciliary care and lacked all the approved facilities needed for the proper treatment of pulmonary tuberculosis. For instance, it had no clinical laboratory, and the occasional sputum examinations were referred to the laboratory of the State Health Department. It had no X-ray department, and physical examinations were checked by radiograms only on exceedingly rare occasions in private laboratories. Artificial pneumothorax treatment or other surgical procedures were never employed.

In the year 1930, with a change in the institutional administration, a definite medical policy concerning tuberculosis control was introduced. It was recognized that the treatment of tuberculosis demands more than provisions of shelter, food and rest for those afflicted, and that the Sanitarium has to be equipped with facilities for the well-recognized and established forms of surgical treatment. Consequently, the institution was equipped with clinical and X-ray laboratories, with facilities for pneumothorax treatment, and finally with an operating room.

The "rest-cure" as such was naturally not abandoned but rather more rigidly enforced than previously. The number of patients, for instance, permitted to go to the dining-room for meals has been decreased almost to the vanishing point.

The ruling that only incipient and moderately advanced cases be admitted and that patients be permitted to stay in the Sanitarium only for one year was discarded. At present, patients in all stages of the

[1] Peoria Municipal Tuberculosis Sanitarium, Peoria, Illinois.

disease are admitted, and they are not discharged before they have reached the maximum benefit from institutional care, or at least until their sputum becomes definitely negative.

The procedures followed by the Chest Clinic have also been systematized. Great care is taken that every member of the household from which a patient is admitted to the Sanitarium be examined for tuberculosis either by the family physician or by the Clinic. A similar procedure is followed in every instance when a death from tuberculosis is reported to the Health Department in a case previously unknown to the Clinic. In these instances the Clinic examination includes routinely the intracutaneous tuberculin test, at least three sputum examinations on twenty-four hour specimens whenever the patient expectorates, stereoscopic radiograms, and a two weeks' temperature record. The cases found negative at the first instance are kept under further observation and examined at repeated intervals for a prolonged time before their case is closed as nontuberculous. On cases referred from noncontact families, an intracutaneous tuberculin test is done routinely and a stereoscopic radiogram is taken on all positive reactors and on those negative reactors who show symptoms (cough, expectoration, fever, etc.) indicating the need of a radiological study.

For follow-up supervision every patient discharged from the Sanitarium has to visit the Clinic at stated intervals. In these cases a radiogram is taken routinely every six months, or oftener if necessary, for a considerable time, and later at least once a year, according to the condition of the patient. The sputum is also examined routinely at every visit as long as the patient expectorates.

The field-nurse employed by the Clinic visits the home of every patient on the "active" list at intervals according to the patient's condition. Once a week she reports verbally to the Medical Director on the condition of every patient visited and receives from him instructions in regard to these cases. Under these conditions the Medical Director is in continuous contact with the discharged patients and keeps them under proper supervision and control.

The policy above outlined has been followed now for the past five years; long enough, we believe, that the work done and the results accomplished may be critically analyzed.

THE PATIENTS ADMITTED TO THE MUNICIPAL SANITARIUM

From January 1, 1930, to December 31, 1934, 759 cases have been admitted to the Sanitarium. Of these 647, or 85.24 per cent, have been

admitted once, while the remaining 112 cases, or 14.76 per cent, have been readmissions comprising 53 individuals. During the 5 years the Sanitarium has taken care, therefore, of 700 individuals.

These 700 patients fall in the following groups:

Sixty-three, or 9 per cent, have been found nontuberculous; 17, or 2.42 per cent, were nonresidents of the city; 137, or 19.57 per cent, were of the childhood type; 6, or 0.85 per cent, had the disease in the extrapulmonary form; 3 stayed in the institution for an insufficient time to establish a diagnosis; and 474, or 67.85 per cent, suffered from pulmonary tuberculosis.

Considering the cases of childhood type, it is enough to state that the great majority of them were contact-cases coming from families where one or more members suffered from pulmonary tuberculosis. They were kept under the usual Sanitarium hygienic-dietetic regimen and permitted to go to the school maintained by the Sanitarium so that they have lost no time in their school career.

The nonresidents will not be considered here because they are of no consequence as far as the city is concerned.

Of the 474 pulmonary cases, 461, or 97.24 per cent, were white, and 13, or 2.76 per cent, were Negroes.

Of the 461 white patients 52, or 11.28 per cent, were admitted to the Sanitarium on more than one occasion, while there were no readmissions among the Negroes.

The Negro and white groups will be discussed separately.

1: THE WHITE PATIENTS

Of the 461 white patients, 203, or 44.03 per cent, were minimal; 56, or 12.14 per cent, moderately and 181, or 39.26 per cent, far advanced; 17, or 3.68 per cent, had pleurisy with effusion, one had haemopneumothorax, one spontaneous pneumothorax, one hilum and one chronic miliary tuberculosis.

Age-Groups

In segregating the patients into age-groups, we distributed them in the following groupings: (1) 0–14 years; (2) 15–44 years; (3) 45 years and over.

Of the 461 patients, 7, or 1.51 per cent, belonged to the first; 383, or 83.08 per cent, to the second; and 71, or 15.4 per cent, to the third age-group.

According to the stage of the disease the age-groups varied as follows (table 1):

1: Of the 203 minimal cases, 2, or 0.89 per cent, belonged to the first; 178, or 87.68 per cent, to the second; and 23, or 11.33 per cent, belonged to the third group.

2: Of the 56 moderately advanced cases, 1, or 1.78 per cent, belonged to the first; 40, or 71.43 per cent, to the second; and 15, or 26.78 per cent, to the third group.

TABLE 1

Distribution according to age-groups

STAGE OF THE DISEASE	AGE-GROUPS					
	0–14		15–44		45 and over	
	Number	Per cent	Number	Per cent	Number	Per cent
Minimal: 203 cases: 44.03 per cent	2	0.89	178	87.68	23	11.33
Moderately advanced: 56 cases: 12.14 per cent	1	1.78	40	71.43	15	26.78
Far advanced: 181 cases: 39.26 per cent	4	2.21	148	81.76	29	16.02
Pleural effusion: 17 cases: 3.68 per cent	0	0	13	76.47	4	23.53
Other forms: 4 cases: 0.86 per cent	0	0	4	100	0	0

3: Of the 181 far advanced cases, 4, or 2.21 per cent, belonged to the first; 148, or 81.76 per cent, to the second; and 29, or 16.02 per cent, belonged to the third age-group.

4: Of the 17 cases of pleurisy with effusion, 13, or 76.47 per cent, belonged to the second; and 4, or 23.53 per cent, to the third age-group.

Distribution by Sex

One hundred and eighty-one, or 39.26 per cent, were males, and 280, or 60.74 per cent were females (table 2).

Of the 181 males, 1 case belonged to the first age-group; 141, or 77.9 per cent, to the second; and 39, or 21.5 per cent, to the third age-group. The one case in the age-group of 0–14 had the disease in the minimal stage.

Of the 141 cases in the age-group 15–44, 54, or 38.3 per cent, were in the minimal; 8, or 5.67 per cent, in the moderately and 70, or 49.64

TABLE 2

Distribution according to sex

SEX	AGE-GROUPS	STAGE OF THE DISEASE									
		Minimal		Moderate		Far Advaneed		Pleural Effusion		Other Forms	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Numb r	Per cent
	0–14: 1 case: 0.55 per cent	1	100	0	0	0	0	0	0	0	0
Male: 181 cases: 39.26 per cent	15–44: 141 cases: 77.90 per cent	54	38.30	8	5.67	70	49.64	7	4.96	2	1.10
	45 and over: 39 cases: 21.50 per cent	13	33.33	5	12.82	17	43.59	4	10.25	0	0
	0–14: 6 cases: 2.14 per cent	1	16.16	1	16.16	4	66.66	0	0	0	0
Female: 280 cases: 60.74 per cent	15–44: 242 cases: 86.43 per cent	122	50.41	33	13.63	79	32.64	6	2.48	2	0.83
	45 and over: 32 cases: 11.44 per cent	12	37.50	10	31.25	10	31.25	0	0	0	0

per cent, in the far-advanced stage of the disease; 7, or 4.96 per cent had pleurisy with effusion; one had spontaneous pneumothorax and one haemopneumothorax.

Of the 39 cases in the age-group 45 and over, 13, or 33.33 per cent, were in the minimal; 5, or 12.82 per cent, in the moderately advanced and 17, or 43.59 per cent, in the far-advanced stage of the disease; and 4, or 10.25 per cent, had pleurisy with effusion.

Of the 280 females, 6, or 2.14 per cent, belonged to the first age-group; 242, or 86.43 per cent, to the second; and 32, or 11.44 per cent, to the third age-group.

Of the 6 cases in the age-group 0–14, one was minimal, one moderately advanced and 4, or 66.66 per cent, were far advanced.

Of the 242 cases in the age-group 15–44, 122, or 50.41 per cent, were in the minimal; 33, or 13.63 per cent, in the moderately advanced and 79, or 32.64 per cent, in the far-advanced stage; 6, or 2.48 per cent, had pleurisy with effusion; one had hilum tuberculosis, and one chronic miliary tuberculosis.

Of the 32 cases in the age-group 45 and over, 12, or 37.5 per cent, were in the minimal; 10, or 31.25 per cent, in the moderately and 10, or 31.25 per cent, in the far-advanced stage of the disease.

Distribution According to Sputum

Of the 461 cases, 256, or 55.53 per cent, had a negative, and 205, or 44.47 per cent, had a positive sputum for tubercle bacilli (table 3).

Of the 256 sputum-negative cases 197, or 76.95 per cent, were in the minimal; 20, or 7.81 per cent, in the moderately advanced and 19, or 7.42 per cent, in the far-advanced stage of the disease; 17, or 6.64 per cent, had pleurisy with effusion; and one each had spontaneous pneumothorax, haemopneumothorax and chronic miliary tuberculosis.

These sputum-negative cases were distributed as follows: 3, or 1.17 per cent, belonged to the age-group 0–14; 208, or 81.24 per cent, to the age-group 15–44; and 45, or 17.58 per cent, to the group 45 and over.

Of the 3 cases in the first age-group, 2, or 66.66 per cent, were in the minimal and 1, or 33.33 per cent, was in the far-advanced stage of the disease.

Of the 208 cases in the age-group of 15–44, 171, or 82.26 per cent, were in the minimal, 13, or 6.26 per cent, in the moderately advanced and 8, or 3.85 per cent, were in the far-advanced stage of the disease; and 13, or 6.26 per cent, had pleurisy with effusion; one had spontaneous pneumothorax; one haemopneumothorax and one chronic miliary tuberculosis.

Of the 45 cases in the age-group of 45 and over, 24, or 53.3 per cent, were in the minimal; 7, or 15.55 per cent, in the moderately advanced, 10, or 22.22 per cent, in the far-advanced stage of the disease; and 4, or 8.88 per cent, had pleurisy with effusion.

Of the 205 sputum-positive cases, 6, or 2.92 per cent, were in the

minimal; 36, or 17.56 per cent, in the moderately advanced and 162, or 79.02 per cent, in the far-advanced stage of the disease; and one had hilum tuberculosis.

These positive-sputum cases were distributed as follows: 4, or 1.95 per cent, belonged to the age-group 0–14; 175, or 85.36 per cent, to the age-group 15–44; and 26, or 12.68 per cent, to the age-group 45 and over.

TABLE 3

Distribution according to sputum

SPUTUM	AGE-GROUP	STAGE OF THE DISEASE									
		Minimal		Moderate		Far Advanced		Pleural Effusion		Other Forms	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Positive: 205 cases: 44.47 per cent	0–14: 4 cases: 1.95 per cent	0	0	1	25	3	75	0	0	0	0
	15–44: 175 cases: 85.36 per cent	5	2.86	26	14.86	143	81.71	0	0	1	0.57
	45 and over: 26 cases: 12.68 per cent	1	3.84	9	34.61	16	61.54	0	0	0	0
Negative: 256 cases: 55.53 per cent	0–14: 3 cases: 1.17 per cent	2	66.66	0	0	1	33.33	0	0	0	0
	15–44: 208 cases: 81.24 per cent	171	82.21	13	6.24	8	3.84	13	6.24	3	1.44
	45 and over: 45 cases: 17.58 per cent	24	53.33	7	15.55	10	22.22	4	8.88	0	0

Of the 4 cases in the first age-group, 1, or 25 per cent, was in the moderately advanced and 3, or 75 per cent, were in the far-advanced stage of the disease.

Of the 175 cases in the second age-group, 5, or 2.86 per cent, were in the minimal; 26, or 14.86 per cent, in the moderately advanced and

143, or 81.71 per cent, in the far-advanced stage of the disease; and 1, or 0.57 per cent had hilum tuberculosis.

Of the 26 cases in the third age-group, 1, or 3.84 per cent, was in the minimal; 9, or 34.61 per cent, were in the moderately advanced; and 16, or 61.54 per cent, were in the far-advanced stage of the disease.

Readmissions

The 53 cases of readmission were all white patients. Of these cases, 48 were admitted twice and 5 three times.

Forty-eight of these patients belonged to the age-group 15–44, and 5 to the group 45 and over.

Thirteen, or 24.52 per cent, were in the minimal; 6, or 11.53 per cent, in the moderately advanced and 30, or 57.69 per cent in the far-advanced stage of the disease; 2 had pleurisy with effusion; and one each had haemopneumothorax and tuberculous peritonitis.

The sputum of 33, or 63.46 per cent, was positive for tubercle bacilli, and of 20, or 36.54 per cent, was negative.

Five of these patients were readmitted for the purpose of a phrenicectomy and 3 returned after their thoracoplasty in a general hospital.

2: THE NEGRO PATIENTS

Of the 13 negro patients, 7 were males and 6 females. One (7.69 per cent) was in the age group 0–14; 11 (84.61 per cent) in the group of 15–44 years; and 1 (7.69 per cent) in the group of 45 years and over.

Two (15.38 per cent) were in the minimal; 1 (7.69 per cent) in the moderately advanced, and 8 (61.54 per cent) in the far-advanced stage of the disease; one had pleurisy with effusion and one had generalized tuberculosis. The sputum of 9 (69.23 per cent) was positive for tubercle bacilli and 4 (30.77 per cent) had a negative sputum.

SURGICAL TREATMENT

1: WHITE PATIENTS

A: Artificial Pneumothorax

There were 130 attempts made. Of these, 92 (70.77 per cent) were successful (included in these were 2 bilateral cases), and 38 (29.23 per cent) were unsuccessful. The 17 cases of pleurisy with effusion were all treated by artificial pneumothorax, as was also the one case of haemopneumothorax and the one of spontaneous pneumothorax.

Of the 90 successful cases (counting the 2 bilateral cases only once), 5 (5.55 per cent) were in the minimal; 20 (22.22 per cent) were in the moderately advanced; and 65 (72.22 per cent) were in the far-advanced stage of the disease (table 4).

Eighty-eight (97.77 per cent) of these cases were sputum-positive for tubercle bacilli, and 2 (2.22 per cent) had negative sputum.

Three (3.33 per cent) were in the age-group 0–14, and the remaining 87 (96.66 per cent) in the age-group 15–44.

TABLE 4

Distribution of surgical treatment

TYPE OF TREATMENT	AGE-GROUPS	SPUTUM	STAGE OF DISEASE							
			Minimal		Moderate		Far Advanced		Pleural Effusion	
			Number	Per cent*	Number	Per cent*	Number	Per cent*	Number	Per cent*
Artificial pneumothorax	0–14	Positive	0	0	1	100	2	66.66	0	0
	15–44	Positive	4	80	16	61.54	65	45.45	0	0
		Negative	1	0.48	1	7.69	0	0	13	100
	45 and over	Negative	0	0	0	0	0	0	4	100
Phrenicectomy	0–14	Positive	0	0	0	0	1	33.33	0	0
	15–44	Positive	0	0	7	26.92	23	16.88	0	0
		Negative	0	0	1	7.69	0	0	0	0
	45 and over	Positive	0	0	6	66.66	6	37.50	0	0

* Per cent of all such cases admitted.

The 5 pneumothorax cases in the minimal stage of the disease comprised 4 (80 per cent) of the sputum-positive cases in this stage in the age-group of 15–44, and one of the 208 sputum-negative cases of the same age-group.

The 18 moderately advanced cases included 16 (61.54 per cent) of the sputum-positive cases in this stage of the age-group of 15–44; one of the 13 sputum-negative cases in the same age-group, and one, that is, the only moderately advanced sputum-positive case in the age group of 0–14.

The 67 far-advanced cases included 65 (45.45 per cent) of the far-advanced sputum-positive cases in the age group 15–44, and 2 (66.66 per cent) of the ones in the age-group 0–14.

B: Phrenicectomy

A total of 66 phrenicectomies have been performed; 10 of these for pleurisy with effusion, and 7 for pleural effusions complicating artificial pneumothorax, that is, 17 (25.75 per cent) for the treatment of effusions, 3 after the lung under artificial pneumothorax was expanded, and 46 (69.69 per cent) for parenchymal lesions.

Of these, 56 (84.84 per cent) had positive and 10 (15.16 per cent) negative sputum. Forty-four (66.66 per cent) had phrenicectomy alone, and 22 (33.33 per cent) had both phrenicectomy and pneumothorax.

Of the 44 who had phrenicectomy alone, 14 (31.81 per cent) were in the moderately advanced stage, and 30 (68.18 per cent) in the far-advanced stage of the disease (table 4).

Of the 14 cases in the moderately advanced stage of the disease, 13 had positive sputum. Seven of these belonged to the age-group 15–44, that is, 26.92 per cent of this group admitted to the Sanitarium; 6 to the age-group 45 and over, or 66.66 per cent of this group cared for in the institution; and one was sputum-negative, belonging to the age group 15–44.

Of the 30 cases in the far-advanced stage of the disease, all had positive sputum. One of these belonged to the age-group 0–14, that is, one of the 3 such cases admitted; 23 to the age-group 15–44, that is, 16.08 per cent of such cases admitted; and 6 to the age-group 45 and over, that is, 37.50 per cent of such cases admitted.

C: Thoracoplasty

Thoracoplasty has been performed in 9 instances. These included 2 cases in which pneumothorax was unsuccessful; one case of pleurisy with effusion refractory to treatment for 3 years; one case of tuberculous empyema, developed in the course of artificial pneumothorax treatment; 2 cases in which only partial pneumothorax could be established; and 3 cases with partial pneumothorax complicated by tuberculous empyema. In all these cases phrenicectomy had been performed prior to the thoracoplasty.

Summary of Surgical Treatment

Counting only one operation in cases in which multiple operations have been performed, we find that surgical treatment was administered (table 5):

1: In the minimal stage to 4 cases (80 per cent) of the sputum-positive group, and to one of the 208 sputum-negative cases.

2: In the moderately advanced stage to 23 (88.46 per cent) of the sputum-positive cases in the age-group of 15–44; to 6 (66.66 per cent) of the same type of cases in the age-group of 45 and over; to one, that is, to the only sputum-positive case in the age-group 0–14; and to 2 (15.38 per cent) of the sputum-negative cases in the age-group 15–44.

TABLE 5

Summary of surgical treatment

AGE-GROUP	SPUTUM	STAGE OF DISEASE							
		Minimal		Moderate		Far Advanced		Pleural Effusion	
		Number	Per cent*	Number	Per cent*	Number	Per cent*	Number	Per cent*
0–14	Positive	0	0	1	100	3	100	0	0
15–44	Positive	4	80	23	88.46	88	61.53	0	0
	Negative	1	0.48	2	15.38	0	0	13	100
45 and over	Positive	0	0	6	66.66	6	37.50	0	0
	Negative	0	0	0	0	0	0	4	100

* Per cent of all such cases admitted.

3: In the far-advanced stage all cases belonged to the sputum-positive group and surgical treatment was given to 3, that is, to all such cases in the age-group 0–14; to 88 (61.53 per cent) in the age-group 15–44; and to 6 (37.50 per cent) in the age-group of 45 and over.

2: NEGRO PATIENTS

There were 3 successful attempts at artificial pneumothorax. These patients belonged to the age-group 15–44, and all had positive sputum: 62.50 per cent of this group of patients were, therefore, treated by artificial pneumothorax.

The one Negro male with pleural effusion was also treated by artificial pneumothorax.

No phrenicectomies have been performed on Negro patients because we could not receive the patient's consent.

THE PATIENTS ADMITTED TO THE CHEST CLINIC OF THE SANITARIUM

During the 5 years from January 1, 1930, to December 31, 1934, 2,460 patients attended the Clinic. This number includes those patients who came to the Clinic for diagnosis, as well as those whose condition has been "followed-up" by the Clinic after their discharge from the Sanitarium (including those discharged prior to 1930). It also includes the following tuberculosis surveys: (1) one of the grade-schools involving about 90 children; (2) of all the children of an orphanage; (3) of Bradley Polytechnic Institute comprising slightly over 40 per cent of the student body; and, finally (4) the survey of the Negro population involving 199 individuals.

Of this number, 2,240 (91.06 per cent) were white and 220 (8.94 per cent) were Negroes. It should be emphasized, however, that 199 of the Negroes included came in the course of a survey when special efforts were made for the examination of the colored population.

In this group, 1,054 (42.84 per cent) were males and 1,406 (57.16 per cent) females.

Of these patients, 944 (38.37 per cent) were children under 15, and the remaining 1,516 cases belonged to the age-group of 15 years and over.

There were 3,033 tuberculin tests made, or 1.23 tests per patient attending.

There were 2,731 sputa examined, or 1.11 sputum examination per patient attending.

During the last 3 years (no separate records have been kept in the first 2 years) 1,459 radiograms were taken on the 1,660 patients admitted during that time, or 0.87 per patient attending.

Sixteen hundred and twenty-three cases (65.97 per cent) were admitted as suspects, and the remaining 837 (34.03 per cent) in the various stages of the disease.

On the 2,460 patients, 6,106 physical examinations were made, or 2.48 examinations per patient attending.

Discharged as nontuberculous 945 (38.41 per cent).

Of the 1,515 cases diagnosed as tuberculous, 57 (3.76 per cent) died of tuberculosis, and 11 (0.72 per cent) of a nontuberculous ailment.

Because they could not be made to coöperate with the Clinic in appearing for an examination, or moved out of town, or changed

address so that they could not be located, 473 (31.22 per cent) were discharged.

The field-nurse made 9,812 calls to the homes of the 2,240 cases, or 4.38 calls per patient attending.

Compilation of the sources whence patients have been referred to the Clinic was started only in the year 1934. Our records for this year show that, of 641 patients (not counting the Negro survey) examined at the Chest Clinic, the largest group, 264 (41.18 per cent) was referred by the family physicians; 107 (16.6 per cent) by the field-nurse; 101 (15.75 per cent) were ex-sanitarium patients; 89 (13.88 per cent) were referred by the public-school nurses; and the remaining 80 (12.59 per cent) were referred by the parochial school nurse, the various welfare organizations and by miscellaneous sources, in the order mentioned.

TABLE 6

YEAR	NUMBER OF DEATHS	HOME CALLS BY NURSE	PER CENT ACCORDING TO A.P.H.A. STANDARDS
1929	65	1736	53
1930	51	1910	74
1931	45	2025	90
1932	36	2272	126
1933	38	1883	100
1934	33	1722	104

The number of home nursing visits, per annual deaths, and the percentage of the visits according to the *Standards* of the American Public Health Association is given in table 6.

It is evident from table 6 that the number of deaths decreased constantly from 1930 on, although the *Standards* of the American Public Health Association were reached only in 1933, and the number of the home-calls increased only slightly.

The number of calls has decreased from 1933 on, because toward the end of 1932 we had to dispense with the part-time clerical help in the office of the Clinic, and from 1933 on our Clinic records were made more extensive and all this work has to be carried on by the nurse.

RESULTS ACCOMPLISHED

1: CHILDHOOD TUBERCULOSIS

Of the 137 patients admitted, 114 have been discharged in a quiescent or arrested condition, and 23 were under treatment on December 31, 1934.

The discharged patients, as a rule, attended or still attend the "Open Window Room Classes" maintained by the Public School System. Their cases are "followed-up" by the Chest Clinic where they appear for examination at stated intervals.

As yet no case of the adult type of the disease was diagnosed in this group.

2: PULMONARY TUBERCULOSIS

A: White Patients

Sufficient time has not elapsed as yet to speak with assurance in all instances of the permanence of the "arrestment" accomplished. We have taken therefore as an indication of favorable results a permanently negative sputum.

It should be emphasized here that the sputum of the patients discharged from the Sanitarium is examined at the Clinic at frequent intervals. The "negative sputum cases" have been proved negative under guinea-pig inoculation, or they have no expectoration.

A conversion from a positive to negative sputum has taken place in 73 cases among the 205 sputum-positive patients admitted, that is, in 35.61 per cent of this group.

These cases were divided as follows: (*1*) *Among the patients on rest-treatment alone:* (a) in the age-group 15–44 in one of the 5 minimal cases (20 per cent), in 4 of the 26 moderately advanced cases (15.38 per cent), in 5 of the 143 far-advanced cases (3.50 per cent), and in the only case of hilum tuberculosis; and (b) in the age-group 45 and over in one of the 16 far-advanced cases (6.25 per cent). (*2*) *Among the patients under surgical treatment:* (a) in the age-group of 0–14, in the only case of moderately advanced tuberculosis, and in one of the 3 far-advanced cases (33.33 per cent); (b) in the age-group 15–44 in 2 of the 5 minimal cases (40 per cent), in 15 of the 26 moderately advanced cases (57.69 per cent), and in 35 of the 143 far-advanced cases (24.48 per cent); and (c) in the age-group, 45 and over, in 2 of the 9 moderately advanced cases (22.22 per cent), and in 5 of the 16 far-advanced cases (31.25 per cent). (*3*) *Total number of sputum conversions from positive to negative:* (a) in the age-group, 0–14, in the only case of moderately advanced tuberculosis, and in one of the 3 far-advanced cases (33.33 per cent); (b) in the age-group 15–44, in 3 of the 5 minimal cases (60 per cent), in 19 of the 26 moderately advanced cases (73.07 per cent), and in 40 of the 143 far-advanced cases (27.97 per cent), and in the only case of

hilum tuberculosis; and (c) in the age-group, 45 and over, in 2 of the 9 moderately advanced cases (22.22 per cent), and in 6 of the 16 far-advanced cases (37.50 per cent). (*4*) *Sputum converted from negative to positive:* (a) in the age-group, 15–44, in one of the 13 moderately and in one of the 8 far-advanced cases; (b) in the age-group, 45 and over, in 3 of the 10 far-advanced cases (30 per cent). The remaining 251 sputum-negative cases have remained negative to date.

THE MORTALITY

1: During Residence

To date (June 1, 1935), of the 461 white patients, 59 died while they were being taken care of in the institution. The institutional mortality was therefore 13.01 per cent. Of these cases, however, 47 belonged to the group of first admissions, giving a rate of 11.52 per cent in this group, and 12 belonged to the group of readmissions giving a rate of 22.64 per cent in the latter.

According to age-groups and stage of the disease, these cases were divided as follows: (1) in the age-group, 0–14, one of the 3 of the far-advanced sputum-positive group (33.33 per cent); (2) in the age-group, 15–44, death occurred in 2 of the 26 sputum-positive moderately-advanced cases (7.69 per cent), in 45 of the 143 sputum-positive far-advanced cases (31.47 per cent), and in one of the 17 cases of pleurisy with effusion (5.88 per cent); (3) in the age-group, 45 and over, in 2 of the 9 sputum-positive moderately-advanced cases (22.22 per cent), in 6 of the 16 sputum-positive far-advanced cases (37.50 per cent) and in 2 of the 10 sputum-negative far-advanced cases (20 per cent).

It is important to consider here the length of residence of these patients in the Sanitarium. Six (10.17 per cent) were in the institution less than one month, 13 (22.03 per cent) less than 3 months, and 21 (35.59 per cent) less than 6 months.

2: After Discharge

In addition to the above, 33 others have died since they left the Sanitarium, bringing the total number of deaths to 92 (19.95 per cent) of the whole group under treatment. Of these 33 additional cases, 28 were admitted once and 5 were readmissions. There were, therefore, 75 deaths (18.33 per cent) in the first-admission, and 17 (32.07 per cent) in the readmission group.

According to age-group and stage of the disease, the total number

of deaths was divided as follows: (1) in the age-group, 0–14, in one of the 3 cases of the far-advanced sputum-positive group (33.33 per cent); (2) in the age-group, 15–44, death occurred in one of the 171 sputum-negative minimal (0.58 per cent), in 5 of the 26 sputum-positive moderately-advanced (19.23 per cent), in 4 of the 8 sputum-negative far-advanced (50 per cent), in 67 of the 143 sputum-positive far-advanced cases (46.86 per cent), and in one of 17 cases of pleurisy with effusion (5.88 per cent); and (3) in the age-group, 45 and over, in 3 of the 9 sputum-positive moderately-advanced (33.33 per cent), in 8 of the 16 sputum-positive far-advanced cases (50 per cent), in 2 of the 10 sputum-negative far-advanced cases (20 per cent).

Of these patients who died, 25 were under artificial-pneumothorax treatment, giving a mortality of 27.77 per cent in this group. Of these, 23 belonged to the 65 sputum-positive far-advanced cases in the age-group, 15–44, a mortality of 35.38 per cent, and 2 of the 16 sputum-positive moderately-advanced cases in the same age-group (12.5 per cent).

Of the 44 patients who had phrenicectomy, 14 died, giving a mortality in this group of 31.81 per cent.

In this group the only case treated by phrenicectomy alone, in the age-group of 0–14, died; one of the 7 moderately-advanced sputum-positive cases in the age-group of 15–44 giving a mortality of 14.28 per cent, 10 of the 23 sputum-positive far-advanced cases giving a mortality of 43.48 per cent in the same age-group, and 2 of the 6 sputum-positive moderately advanced cases (33.33 per cent) in the age-group of 45 and over.

B: The Negro Patients

Of the 13 Negro patients admitted, 7 (53.84 per cent) died in residence at the Sanitarium, and one died after she left the institution, giving a total mortality of 61.54 per cent.

Of these, one belonged to the age-group, 0–14, who had generalized tuberculosis, the only such case admitted; 6 belonged to the age-group, 15–44, and to the sputum-positive far-advanced group, that is, 75 per cent of the 8 patients belonging to this group and the one sputum-positive far-advanced case admitted belonging to the age-group, 45 and over.

In this group, 3 were under artificial-pneumothorax treatment and they all died.

Deaths from Pulmonary Tuberculosis in the City of Peoria

During the 5 years from January 1, 1930, to December 31, 1934, 201 residents of the city died of tuberculosis (all forms), and 180 (89.55 per cent) of pulmonary tuberculosis, as far as we could trace them. Of the deaths from pulmonary tuberculosis, 59 (32.22 per cent) occurred in the Sanitarium; 23 (12.78 per cent) in the State Hospital in Bartonville, Peoria County; and 5 (2.78 per cent) in the Hospital of the County Farm. In all therefore, 86 (47.77 per cent) of these deaths occurred in institutions, while the remaining 94 (52.23 per cent) occurred in homes.

Of the 201 deaths 20 (9.95 per cent) were Negroes, while according to the 1930 Census the Negro population amounted to only 2.89 per cent. The number of Negro deaths was therefore 3.44 times higher than the Negro ratio in the City's population.

Of the 180 deaths from pulmonary tuberculosis, 112 (62.23 per cent) belonged to the age-group, 15–44, and 68 (37.77 per cent) to the age-group, 45 and over.

The one child who was admitted to the Sanitarium in the age-group, 0–14, and died there, reached the age of 15 by the time of her death and is included among the deaths in the age-group, 15–44.

The Mortality from Tuberculosis in the City of Peoria

Chart 1 presents the number of resident deaths from tuberculosis (all forms) from the year 1920 to 1935, for the City of Peoria, showing that the number of deaths decreased from 65 in 1929 to 33 in 1934, or a reduction of 49 per cent.

The computation of the figures for the decade, 1920–1929, inclusive, was a formidable task, because they had to be collected from 4 sources: (1) the number of those who died within the City limits, exclusive of those nonresidents who were brought into the general hospitals from out of town; (2) those residents who died at the Municipal Tuberculosis Sanitarium, and who, because the institution is located outside of the City limits in Richwood Township, were charged in the Official Vital Statistics to the County and not the City; (3) those residents who died at the Peoria State Hospital located in Bartonville, Illinois, in Peoria County; and, finally (4), those residents who died at the Hospital of the County Farm located in Limestone Township outside of the City.

For the purpose of computation the copies of the death-certificates of the City of Peoria, Richwood and Limestone Townships, filed in the offices of the respective registrars, were studied, and a copy was made of

every certificate giving tuberculosis as the cause of death or as a contributing cause. A study was also made of the death-records of the State Hospital and a copy made of the tuberculosis deaths. These studies were conducted by Mr. Andrew Haeflin, a senior student at the Sociology Department of Bradley Polytechnic Institute. From January 1, 1930, on, a copy of every death-certificate registering tuberculosis as primary or secondary cause of death and filed with the registrar of the City is filed in the office of the Chest Clinic. A similar procedure is followed in the case of every death of the patients registered with this Clinic, even if the cause of death is not given as tuberculosis. A list of deaths from tuberculosis of the patients of the State Hospital and of the County Farm is received at the close of each year. From the

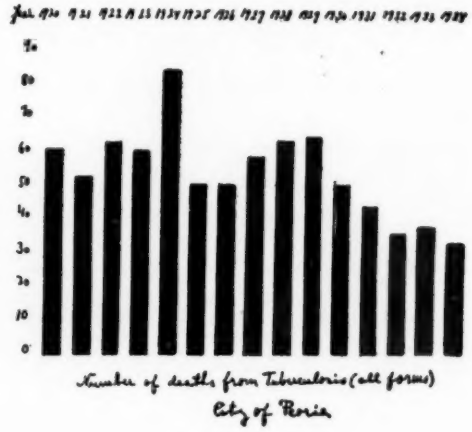

CHART 1

records of the Municipal Sanitarium and from these sources the number of resident deaths is then computed. It should be emphasized that every death of a former resident Sanitarium or Clinic patient occurring outside of the City limits is also included in this computation whenever we learn of it. It should be mentioned here that it has happened in a number of instances that in the case of some of our former patients, when we had every evidence that they were suffering from far-advanced pulmonary tuberculosis, the cause of death was given as a nontuberculous pulmonary disease, as, for instance, bronchial asthma, bronchiectasis, lung abscess, when their death occurred outside of our institution. These cases were included among the tuberculosis deaths in our computation.

It is also of interest to note that the death-certificates signed by the general practitioners only relatively seldom state, under the question what tests have confirmed the diagnosis, that it was confirmed by sputum or X-ray examinations. There are instances on record in which the patient was attended for only two or three days and the cause of death was given as pulmonary tuberculosis without the sputum having been examined. It is evident that, under these conditions, the correctness of the diagnosis could be questioned in many instances. Nevertheless, we had to accept the diagnosis as it stood on these certificates.

Chart 2 presents the number of deaths from pulmonary tuberculosis. As might be seen at a glance, close correlation exists between the num-

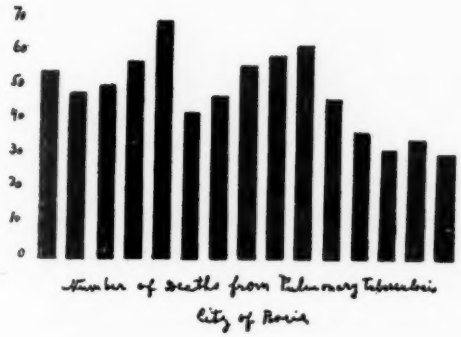

CHART 2

ber of deaths from tuberculosis, all forms, and of those from pulmonary tuberculosis. Both charts show the interesting similar characteristics. In the decade, 1920 to 1929, no definite trend is discernible. In this decade the peak was reached in the year 1924. This year is outstanding, especially alongside the low height of the succeeding years, 1925 and 1926. No definite reason can be given for this sudden rise. If the average number of deaths for the 3 years, 1924 to 1926, is figured, however, it is found to be 62 for the deaths, all forms, and for pulmonary tuberculosis 53, making the heights of these years fairly even. It might be assumed, therefore, that for some reason or other some people have died of tuberculosis in the year 1924 prematurely, whose death should have occurred in the succeeding 2 years.

From the year 1930 on, there is a definite downward trend noticeable. The decrease in the number of deaths from pulmonary tuberculosis was from 63 in 1929 to 47 in 1930, or 25 per cent, and 31 in 1934, or 50 per cent, respectively. In the last 5-year period there is a slight peak in 1933. This peak, however, is due to the fact that during that year there were 7 Negro deaths, an unusually large number in relation to the Negro population, and to be compared with 2 Negro deaths in the year before and with one in the succeeding year.

Chart 3 is a composite, showing the mortality rates of tuberculosis (all forms) for the State of Illinois, down State, Illinois (exclusive of the City of Chicago), the urban rate for cities with a population of 10,000 and over, and finally the rural rate.

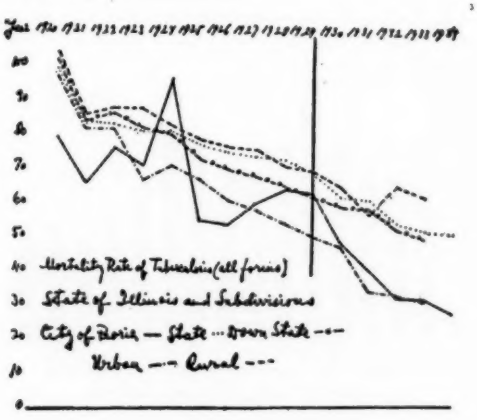
Mortality Rate of Tuberculosis (all forms)
State of Illinois and Subdivisions
City of Peoria — State ··· Down State -·-
Urban —·— Rural ---

CHART 3

As far as the rate for the City of Peoria is concerned, no definite trend can be discerned for the decade prior to the year 1930, and a very definite downward trend is seen during the 5-year period for 1930–1934. The decrease for these 5 years was from 64 per 100,000 population in 1929 to 28 in 1934, or 56 per cent.

It is also evident from chart 3 that the rate for the City declined more steeply than that of the other subdivisions. The rate for the State, for instance, decreased from 70 in 1929 to 52 in 1934, or 26 per cent, as against 56 per cent for the City of Peoria. It is also of interest to note that in 1932 the rate for the City reached the urban rate, the lowest among all the subdivisions.

Chart 4 shows the mortality rate of pulmonary tuberculosis for the

City of Peoria, State of Illinois and down State, for the last 2 political divisions only to the year 1933, because at this writing no more recent data are available.

It is evident from this chart that the death-rate for pulmonary tuberculosis of the City of Peoria decreased from 62 in 1929 to 27 in 1934, or 56 per cent, while, in the decade before, the decrease was from 72 in 1920 to 62 in 1929, or 14 per cent. It is also evident that the mortality for the City in the last 5 years decreased considerably more than that for the State and down State. The decrease for the State of Illinois was 23 per cent, for down State 21 per cent, and for the City 50 per cent from 1930 to 1933.

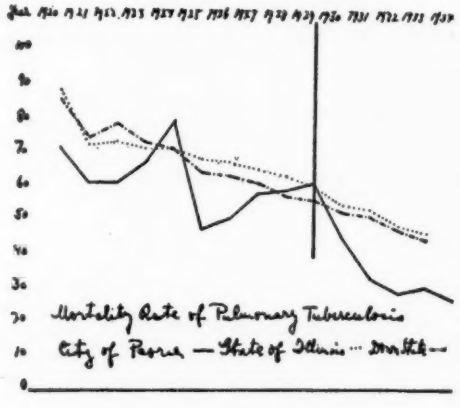

CHART 4

Chart 5 gives the mortality rate of pulmonary tuberculosis for the age-groups, 15 to 44, and 45 and over.

The rate was not computed for the group, 0–14, because the number of deaths in this age-group was small and the variations entirely irregular. In the decade from 1920–1929, the number of annual deaths in this age-group varied from zero to 11 in the year, 1924. It was twice 1, 3 times 3, once 4, 5 and 6, respectively. The total number of deaths during these 10 years in this age-group was 37.

In the 5 years from 1930–1934, in one year there was no death in this age-group and twice it was 1 and 2, respectively. The total number of deaths was 6.

Figuring these deaths in 5-year periods, there were 24 deaths in the years, 1920–1924; 13 in the years, 1925–1929; and 6 from 1930–1934.

There was therefore a reduction of 54 per cent in the 5-year period of 1930–1934 as compared with the previous 5 years.

As it might be seen from chart 5, the mortality was lower in the younger age-group until the year 1933, and, in that year and in the following, it approached that of the higher age-group. In 1933 this elevation was caused by the large number of Negro deaths, but in 1934 there was an increase in white deaths.

The mortality of pulmonary tuberculosis was reduced from 67 in 1929 to 34 in 1934, or 49 per cent, in the younger age-group, and from 96 to 34, or 64 per cent, in the higher age-group.

Chart 6 shows the mortality curve of tuberculosis (all forms) and of pulmonary tuberculosis for the white population.

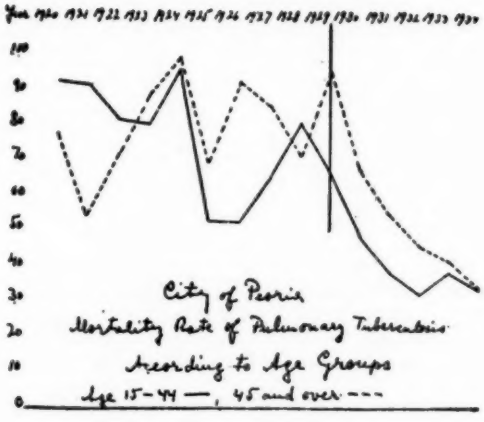

CHART 5

Comparing this chart with chart 3, we find that the curve of tuberculosis (all forms) of the white population was, until the year 1934, considerably lower than that of the general population. In 1934 both curves reached the same level. The general rate was 64 in 1929 and 28 in 1934, while the white rate was 57 in 1929 and 28 in 1934. From 1929 to 1934 there was therefore a reduction of 51 per cent in the mortality rate of tuberculosis (all forms) in the white population, while it was 56 per cent for the general population.

Comparison of chart 6 with chart 4 shows a similar situation. The general rate was 62 in 1929 and 27 in 1934 and the white rate was 56 in 1929 and 27 in 1934. The decrease in the white rate was therefore 51 per cent in the last 5 years, against 50 per cent in the general rate.

Chart 7 shows the mortality curve for pulmonary tuberculosis according to the two age-groups for the white population.

It is evident that the rate for the younger age-group is considerably lower until 1934 when it for the first time exceeded the higher age-group.

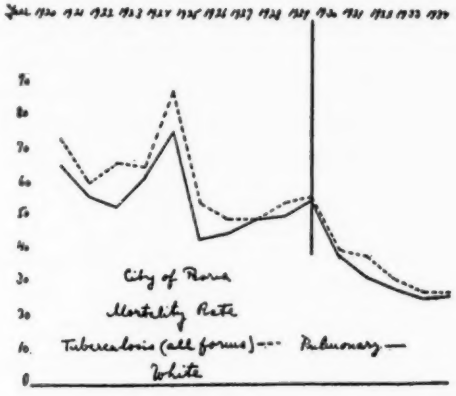

CHART 6

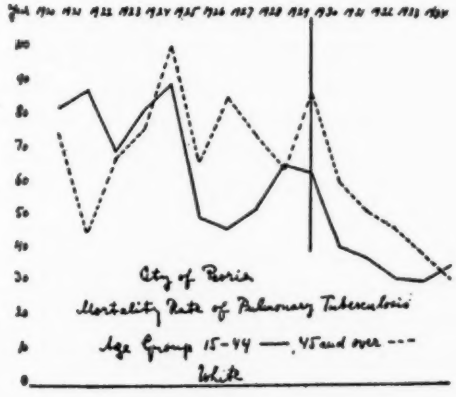

CHART 7

The decrease in the younger age-group was from 64 in 1929 to 36 in 1934, or 43 per cent, and in the older age-group from 87 in 1929 to 31 in 1934, or 64 per cent.

The rate of the younger age-group shows an increase from 31 in 1933 to 36 in 1934, or 16 per cent.

The mortality curve for the Negro population was not plotted on account of the small number of deaths and the irregularity of the trend. The number of deaths from tuberculosis (all forms) in the decade, 1920 to 1929, in the Negro group varied annually from 3 to 12, and in the 5 years, 1930 to 1934, from 1 to 8. Figuring the deaths from tuberculosis (all forms) in 5-year periods, there were 36 in the period, 1920–1924, 40 in 1925–1929, and 20 in 1930–1934, or a 50 per cent reduction in the last 5 years.

For pulmonary tuberculosis the number of deaths was 29 in 1920–1924, 38 in 1925–1929, and 17 in 1930–1934, giving a reduction of 55 per cent in the last 5-year period.

DISCUSSION

The medical procedures followed by our institution and outlined in this paper do not need further justification here. Every well-conducted tuberculosis sanatorium follows the same principles. Yet, one still often finds tuberculosis sanatoria maintained from public funds which have no clinical or X-ray laboratories and are not equipped even for the simplest form of collapse therapy, as, for instance, artificial pneumothorax. State laws, county and city ordinances which provide for the care of the tuberculous, and legislatures, County Boards of Supervisors and City Councils which appropriate funds for these institutions, seldom make requirements concerning the medical standards. From the standpoint of the community and the taxpayers, however, who foot the bills for the expenditures, a poorly equipped and managed institution does not bring the returns in the improvement of public health which the taxes spent on sanatoria should earn.

The question, whether really far-advanced and hopeless cases promising no possibility for improvement, be admitted to a sanatorium, is often debated. But, considering the fact that these cases are a menace to their environment and to the community, makes their admission to a public institution imperative. In admitting cases to a hospital for contagious diseases it is never questioned whether a given case will recover or not. Why should this distinction be made in the case of tuberculosis which is just as contagious as any other infectious disease? Tuberculosis sanatoria and hospitals serve just as well the purpose of isolation as that of treatment. And, from the standpoint of the community, is not the former as important as the latter in preventing the spread of the disease?

The period for which patients are kept in institutions varies with the different sanatoria. We believe that no definite time-limit can be set for the length of stay of the individual patient. The fundamental principles, however, we feel can be safely stated as guides in this direction. The patients should be kept in an institution for the time necessary to reach the maximum benefit from sanatorium care, or at least until their sputum becomes definitely negative, so that they will not become again a menace to their environment or community after they will be discharged.

The number of patients who were found not to suffer from tuberculosis was 9 per cent. In her study on *Tuberculosis Hospitalization in the United States* (1), Miss Whitney found the same percentage. This fairly high percentage is due to the fact that patients are admitted to the institution at the recommendation and upon the diagnosis of the family physician, who without the proper aid of X-ray and other facilities, is not always in a position to render a correct diagnosis. These cases include bronchiectasis, lung tumors, massive pulmonary atelectasis, etc. Such instances cannot be avoided. The differential diagnosis between tuberculosis and other pulmonary diseases is often a very difficult procedure, calling for prolonged observation and the aid of X-ray studies, etc. In some of these cases death has occurred while the patient stayed at the Sanitarium. In every such instance, we were fortunate enough to receive permission for a postmortem examination and the clinical diagnosis was corroborated by autopsy.

The ratio of patients with extrapulmonary disease, 0.85 per cent, is exceedingly small. Patients suffering from extrapulmonary tuberculosis do not always find their way to tuberculosis sanatoria.

The large proportion of children (19.57 per cent) suffering from the childhood type of the disease were found chiefly through the activities of the Chest Clinic by investigating all the contact cases, particularly children. We consider this as one of the important preventive activities of the institution. Miss Whitney (1) reports only 8 per cent for the United States, but it has to be considered that a great number of sanatoria have no provisions for the care of the childhood type.

The number of Negro patients was small, yet their percentage corresponds to the percentage of the Negro population of the City.

The percentage of the minimal cases, 44.03 per cent, is high, when compared to the percentage of 16 given by Miss Whitney (1). A great number of our cases had only some of the following characteristic symp-

toms of pulmonary tuberculosis, such as fatigue, loss of weight, low-grade fever, localized increase in lung markings on the X-ray film, but no percussive or auscultatory findings or definite parenchymal lesions by X-ray. It may well be that some of them had no pulmonary involvement. The care of such patients, however, cannot be entirely avoided if we set our intention on early diagnosis and the prevention of the disease. This relatively large number speaks well for the alertness of the practising physicians of our community in making every effort for an early diagnosis, and is also the result of the work of the Chest Clinic in systematically examining every contact case by submitting to a thorough examination every member of a household from which a patient is admitted to the Sanitarium, or a death from tuberculosis is reported to the Registrar of Vital Statistics.

We have made up our age-groups arbitrarily in order that we might have large enough numbers in the different groups, which will permit the plotting of mortality curves, and we intended to have the age-grouping of the patients in conformity with that of the curves.

The percentage of the age-group, 0–14, is very small. This is due, no doubt, to the fact that, as yet, no systematic efforts have been made for the survey of the apparently healthy children of school-age.

The percentage (83.08 per cent) of the age-group, 15 to 44, is alarmingly high. It shows that the largest number of our patients is still recruited from the most productive group of society, the 'teen ages, the young adults and the middle-aged.

The percentage division was maintained also in the relative proportion of these age-groups in the various stages of the disease. It should be emphasized, however, that the percentage of the first age-group was relatively high in the far-advanced group, 2.12 per cent.

The females far outnumbered the male patients. The preponderance of tuberculosis among women has been made a subject of study by various authors. As yet, no definite answer has been found to this puzzling problem. We are inclined, however, to believe that the extensive employment of young girls in gainful occupations coupled with the "modern" way of life in their most formative years is a factor in this preponderance. The fact that the percentage of women in the age-group, 15–44, was 8.53 per cent higher, and in the age-group, 45 and over, 9.96 per cent lower than that of men may lend some support to this assumption.

It is of interest to note that in the two higher age-groups the percentage of the minimal cases was considerably higher and that of the far-

advanced cases considerably lower among the women than among the men. The majority of the girls in the first age-group, however, belonged to the far-advanced group.

The majority of the cases had negative sputum, 55.53 per cent. The majority of these, 76.95 per cent, were in the minimal, and only a small percentage, 7.42 per cent, were in the far-advanced stage of the disease. It is of importance, however, that the largest percentage, 22.22 per cent, of far-advanced cases was in the highest age-group, 45 and over.

The largest percentage of the sputum-positive cases was in the far-advanced stage of the disease, 79.02 per cent. This fact shows that a very large number of patients are permitted to reach the far-advanced stage without having their sputum examined.

A study (2) conducted on 100 cases, a part of which comprised all the pulmonary patients who were inmates at that time of the Sanitarium and the remainder selected at random from our out-patient pneumothorax clinic, has shown that 43 patients of the 100 had no sputum examination before they entered the Sanitarium.

There is an apparent contradiction between the fact that so many of our cases were in the minimal stage of the disease, and yet in another large group the examination of the sputum was neglected and these cases were permitted to reach the far-advanced stage. It shows, we believe, that while the general practitioner thinks of tuberculosis when the complaints of the patients are vague, and consist of low-grade fever, fatigue, loss of weight and similar symptoms, he forgets the possibility of tuberculosis when definite respiratory symptoms are present which permit the diagnosis of such trivial diseases as "cold," bronchitis, etc.

In the study referred to above, in 43.39 per cent of the cases the initial symptoms were those of an acute respiratory disease, and in an additional 26.41 per cent a productive or unproductive cough. Yet the sputum was only seldom examined because tuberculosis was not considered.

The 53 cases of readmissions comprised 8.69 per cent of the 461 white patients treated for tuberculosis. It is of interest to note that the majority of them had the disease in the far-advanced stage and 63.46 per cent had a positive sputum.

The majority of these patients left the institution against medical advice during their previous stay. A few of them, because they had to take care of their family affairs, but the most of them because they objected to the restricted life of an institution.

Considering the high mortality of the Negro race, the number of

Negro patients was surprisingly small. It seems to us that there is an unwarranted indolence in this group toward health matters. With one of the objects to create a greater interest in this group toward the control of tuberculosis, with the help of the Civil Works Administration we carried on a survey of the colored group during the winter months of 1933–1934, but except for finding a few cases suffering from tuberculosis, the survey did not bring the desired results, and in the past year we have seen no increased attendance of Negroes at the Clinic. It should be emphasized that in our work no discrimination is made against the Negro and that they are handled in every respect with the same care as are our white patients and receive the same accommodations.

We did not use artificial pneumothorax in the oldest age-group, 45 and over, because we were greatly concerned with the strain under which the pulmonary collapse puts the heart, and we resorted to it in the sputum-negative group only in exceptional cases, because we feel that the complications which may arise in the course of pneumothorax treatment warrant the avoidance of this treatment when there is a great likelihood that the patient will improve without it.

On the other hand, in the sputum-positive group we made every effort to collapse the lung whenever the disease was not so far advanced bilaterally that a successful collapse would have endangered life.

Under these conditions, the fact that 19.52 per cent of our cases were under pneumothorax treatment shows that this form of treatment was extensively used.

An attempt for collapse was made in 61.46 per cent of the sputum-positive group and the attempt was successful in 42.92 per cent of all the sputum-positive cases. Considering the fact that the sputum-positive cases include a large number of bilaterally far-advanced cases, this percentage, we believe, is fairly high.

We are in full agreement with Myers and Levine (3) that artificial pneumothorax should be applied in the minimal stage of the disease, as seen from the fact that in 80 per cent of our sputum-positive minimal cases this procedure has been applied. We restrict pneumothorax, however, as stated above, to the sputum-positive group.

Phrenicectomy has been performed irrespective of the patient's age. The oldest of our patients was 60 years old, who, although the paralysis was complete and his diaphragm rose 2 in., had not the slightest discomfort.

A phrenicectomy was performed in every instance in which an at-

tempt for pneumothorax was unsuccessful and the patient consented to the operation. It was also resorted to in every case of the age-group, 45 and over, when collapse therapy seemed to be indicated. Thus 12 cases (46.15 per cent) of the 26 admitted in this age-group with a positive sputum received this form of treatment.

In the aggregate, 134 (29.06 per cent) of our pulmonary cases, and 131 (63.90 per cent) of the sputum-positive group received some form of surgical treatment.

It is of interest to note that, outside of the survey conducted among the Negro population, only a negligible number, 21 Negroes, attended the Clinic.

The number of females attending the Clinic was 14.32 per cent higher than that of the males.

We found the tuberculin test a valuable aid in "screening-out" tuberculosis not only in children but also in adults. It is of significance that, of 251 apparently healthy college students, 56 per cent reacted negatively to 0.10 cc. of a dilution of 1:100 O. T. On the other hand, we had two negative reactors in the far-advanced stage and with positive sputum and one negative reactor with tuberculosis of the spine in whom 2 vertebrae were markedly destroyed. A negative tuberculin test, therefore, is not infallible when the resistance of the body is exhausted in the late stages of the disease.

The fact that 65.97 per cent of the attending patients have been suspects shows that the Clinic is widely used for the purpose of diagnosis.

The fact, as is shown by one sample year of 1934, that the medical profession referred the largest group, 41.18 per cent, of the patients to the Clinic shows that practising physicians appreciate the value of and fully coöperate with the Clinic. The family physician being the most important factor in the early diagnosis of tuberculosis, the value of this coöperation cannot be overemphasized.

In our experience we found the specialized nursing service, standing under the direction and the immediate supervision of the Medical Director, far more effective than the generalized service practised in our city prior to the year 1930. We find that by this arrangement the examination of the contact cases can be more easily directed, and that the follow-up and supervision of the patients discharged from the Sanitarium are more effective. Tuberculosis nursing is after all only one phase of tuberculosis control, and its segregation under different direction from that of the other phases leads to unnecessary complications in

administration, and deprives the Sanitarium physicians from the immediate supervision of their former patients.

This point needs special emphasis, because, since the National Organization for Public Health Nursing has taken a definite stand for generalized service, its representatives use every means, as we had chance to observe, when an occasion presents itself, to persuade communities to change from specialized to generalized service, even if the former has proved effective.

It has been our experience, further, that the number of the nursing visits *per se* is not as important as the fact that the calls should serve a definite purpose and be individualized. Some patients need a closer and more frequent supervision than others: the less intelligent need more instruction, the less coöperative more frequent persuasion, etc. The number of calls to the patients has to be directed according to the individual needs and not by a set figure.

The number of sputum conversions from negative to positive 73 (35.61 per cent) is, we believe, fairly high. We believe that this fair result was achieved through the extensive use of surgical measures.

It is of significance that, of the 256 sputum negative cases, only 5, that is, less than 2 per cent became sputum-positive while residing in the Sanitarium.

It is noteworthy that the percentage of institutional deaths was twice as high in the readmission than in the first-admission group. As the majority of readmission patients had left the institution against medical advice during their first stay, it is reasonable to assume that a number of these deaths might have been prevented by a greater coöperation on the part of these patients.

It is of importance that more than one-third of the patients who died during their stay in the institution had been under the care of the Sanitarium for less than six months. It is obvious that they must have been admitted in the terminal stage when therapeutic efforts were of little avail.

A few of the deaths deserve special consideration. The one minimal sputum-negative case in the age-group, 15–44, refers to a 17-year-old girl in the readmission group, who at the time of her first admission spent 62 days in the institution, leaving against advice and returned a year later in the moderately-advanced stage but still sputum-negative. After less than 3 months she left again against advice, and 2 years later she died of generalized tuberculosis.

Of the two sputum-negative far-advanced cases who died in the Sanitarium one was a 60-year-old woman, admitted to the institution 3 times. The first time she spent 11 days there; a year later she was admitted again and stayed for 8 months and was still sputum-negative; two years later she was admitted with a positive sputum and died 2 months later. The other case was a 62-year-old man who died after a 2 weeks' stay.

The case of pleurisy with effusion died of tuberculous meningitis.

The fact that a relatively large percentage of the cases under surgical treatment died shows that we have used collapse therapy often as a last resort and could accomplish only alleviation of symptoms for a certain time. In the moderately advanced group at times we were unable to prevent the progression of the disease even under artificial pneumothorax, as shown by serial X-ray films and postmortem findings.

The evaluation of results in the treatment of tuberculosis, as in every other chronic ailment of long duration, in which relapses follow cycles of apparent well-being, is an exceedingly difficult and often a very unreliable procedure. Moreover in tuberculosis, in which the "constitution" and "resistance" of the individual play such an important part in recovery, every case is a law to itself, so that control groups in comparing the value of different therapeutic procedures are of no value.

We feel, however, that the changes in the mortality of large population groups constitute an important index from which, other factors remaining equal, the influence of our control measures can fairly well be judged. Rosenfeld in his study on *Tuberculosis Statistics* comes to the conclusion that "Statistics (mortality) . . . . may give a solid basis for researches tending to the discovery . . . . of the causes of variation of tuberculosis mortality" (4).

We are aware of the fact that the computation of mortality statistics for the City of Peoria, as presented, has many shortcomings. Obviously the State Department of Health, through its Bureau of Vital Statistics, is the only organization in the State which is in a position to compile accurate data on the mortality of the various communities through the proper allocation of deaths. Such compilations would be of paramount importance to the various governmental subdivisions in the evaluation of the magnitude of their tuberculosis problem and of the effects of tuberculosis-control measures practised by them. As things stand today, however, the counties maintaining tuberculosis sanatoria and the ones which have mental and penal institutions located within their

boundaries, are at a great disadvantage when the figures of the official *Vital Statistics* are computed, as compared with those which do not make any provisions for the proper care of their tuberculous residents and which are not charged with the burden of the deaths of nonresidents in the various institutions. These deaths at times are numerous, so that they unfavorably influence the respective mortality curves. Under these conditions the present official *Vital Statistics*, as far as certain counties and cities are concerned, rather distort the actual facts than present the true situation, and cannot be used therefore for the purpose they should serve.

However, as long as the errors committed in our compilation have been identical in the annual computations and as long as our deductions are based, not as much on the absolute figures as on the proportion of the reduction in the rate, we feel that our conclusions are fairly well justified. It should be emphasized that for the decade, 1920–1929, no corrections have been made which would increase the figures of the official *Vital Statistics*, while for the 5-year period, 1930–1934, a great number of deaths has been added to the officially recorded figure. The comparison of the two periods is therefore more favorable for the decade, 1920–1929, than for the period of 1930–1934.

During the depression much has been said and written about the exodus from cities to the country. Until a new census is taken, it will be impossible to determine the exact magnitude of this population movement in the various communities. It is, however, the opinion of various observers that, due to the great variety of its industries, the City of Peoria has continued to show gradual growth, as it did in the decade prior to 1930. The fact that the number of registered voters increased 6,147 between the presidential years of 1928 and 1932 lends considerable support to these observations.

All the charts presented show a decided and continued decrease in mortality from the year 1930 on, in contrast to the previous decade. While the depression, starting in 1930, has brought with it a definite change in the social environment of our City, it cannot be assumed, we believe, that the elimination of health hazards, through the elimination of industrial hazards which endanger health, can be made responsible for this sudden decrease. On the other hand, the definite and drastic changes made in the methods of tuberculosis control in the same year and carried on continuously since then, we believe, can be justly assigned as the cause of this decrease in the number of tuberculosis fatalities.

The fact that the mortality curve of the City of Peoria shows a sudden change in the year 1930, while the curve of the State of Illinois and its various subdivisions continued to show the same trend as before, adds further justification to this assumption.

A few words have to be said here of the curves of the various subdivisions of the State of Illinois. The fact, that the urban rate is the lowest among the various divisions and the rural is the highest, is well explained by the location of tuberculosis sanatoria, mental hospitals and penal institutions. These institutions which annually contribute a large number of deaths from tuberculosis are, as a rule, located in rural districts and are seldom found within the boundary lines of the cities. As long as the deaths occurring in these institutions are not allocated to the residences of the inmates, obviously they swell the mortality of the subdivisions where these institutions are located and lessen proportionately that of the urban areas to which these deaths should justly be charged.

The change in the mortality curve of the age-group, 15–44, toward an upward trend in the year 1934 might be attributed to two causes, that is, either to the effects of the depression or to the increase in industrial employment (or to both factors). It remains to be seen in the coming year whether this change will be only temporary or remain permanent. At any rate, it calls for increased efforts and added vigilance in our measures of control.

The large number of Negro deaths registered in our City as elsewhere throughout the country is a problem of great importance. While the decrease in the Negro deaths shows a decrease proportionate to that of the white race in our City, nevertheless special measures are needed to reduce the Negro mortality towards the level of the white. Such an attempt has been made in our community by a survey conducted through the winter of 1933–1934. While this disclosed some cases suffering from tuberculosis, it failed to promote a greater interest toward tuberculosis in the Negro race, as proved by the fact that the number of Negroes utilizing the facilities of the Sanitarium and the Clinic is just as small now as it was before the survey was conducted.

While we feel that the mortality curves prove that our tuberculosis-control measures have contributed greatly to the reduction of tuberculosis fatalities in our community, it is impossible to assign a definite share in this reduction separately to each one of these measures. The important results of our tuberculosis control measures as brought out

in this study were as follows: (1) the diagnosis of a large number of minimal cases; and (2) of large number of sputum-negative cases; (3) the protection of sputum-negative cases from progression into positive-sputum cases; and (4) the conversion of sputum-positive cases into negative ones.

The diagnosis of the minimal and sputum-negative cases was effected by the close coöperation of the practising physicians and the Sanitarium, on the one hand, and by the examination of the contact cases through the Clinic, on the other. Sanitarium care was instrumental in the protection of the patients, as demonstrated by the fact that less than 2 per cent of the sputum-negative cases became positive. The extensively used surgical measures contributed greatly to the fairly large number of sputum conversions from positive to negative. The supervision of the discharged Sanitarium patients through the Chest Clinic was an important factor in preventing the "break-down" of these patients.

No matter how desirable certain public-health aims are, their materialization will be limited by the financial resources available. It is of importance, therefore, to state that the expenditures of the Sanitarium and the Clinic were not increased by the introduction of the more effective control measures. On the contrary, due to the shrinkage in taxes on account of the depression during the last five years, the annual income decreased considerably. Yet, by the practice of economy, we were enabled to provide our institution with new and adequate equipment, and maintain it in an improved condition of repair.

CONCLUSIONS

1. An analysis of the patients cared for in the Municipal Sanitarium and Chest Clinic of a city in the 100,000-population class (Peoria, Illinois) during the 5-year-period, 1930–1934, and the mortality curves during the 15 years 1920–1934, are presented.

2. The mortality curves show that from 1929 to 1934

a. The number of deaths from tuberculosis (all forms) decreased 49 per cent.

b. The number of deaths from pulmonary tuberculosis decreased 50 per cent.

c. The mortality rate of tuberculosis (all forms) and of pulmonary tuberculosis decreased 56 per cent.

d. The mortality rate of pulmonary tuberculosis decreased 49 per cent in the age-group, 15–44, and 64 per cent in the group, 45 and over.

e. The number of deaths in the age-group, 0–14, decreased 54 per cent, as compared with the previous 5-year-period.

f. The mortality rate of the white population decreased 51 per cent both from tuberculosis (all forms) and from pulmonary tuberculosis.

g. The mortality rate of the white population decreased 43 per cent in the age-group, 15–44, and 64 per cent in the group, 45 and over.

h. The number of Negro deaths from tuberculosis (all forms) decreased 50 per cent in the last 5-year-period, as compared with the previous 5 years, and from pulmonary tuberculosis 55 per cent.

3. While it is impossible to assign a definite share in this reduction individually to the various control measures, it is believed that all of them played a part in bringing about the favorable results.

The essential factors in this control are

a. The mutual coöperation between the general practitioners and the Sanitarium and the Clinic;

b. The extensive use of X-ray and sputum examinations in diagnosis and in the guidance of treatment;

c. The examination of contact cases;

d. The wide application of collapse therapy;

e. The extended length of stay of the patients in the Sanitarium until they reached the maximum benefit from treatment and until their sputum became negative;

f. The supervision of patients discharged from the Sanitarium.

4. A specialized tuberculosis nursing service, centralized under the direction of the authorities charged with the control of tuberculosis, is most effective in securing the early diagnosis of contact cases and in safeguarding the results accomplished by Sanitarium treatment.

5. The introduction of these effective measures did not increase the financial expenditures of the antituberculosis work.

6. The increase in the mortality of the white population in the age-group, 15–44, during the year 1934 calls for added vigilance in the coming years.

7. By establishing proper medical standards in those public sanatoria which at present are equipped only for domiciliary care, the number of deaths from tuberculosis could be materially reduced.

I wish to express my thanks and appreciation to Mr. Andrew Haeflin for his assistance in studying the death certificates from which the mortality curves have been computed.

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PULMONARY ASBESTOSIS AND CARCINOMA

Report of a Case with Necropsy Findings[1]

DAN S. EGBERT AND ARTHUR J. GEIGER

Although there is a steadily growing recognition of pulmonary asbestosis as a disease entity and industrial hazard, the number of reported cases is still small. In a recent review by Egbert (1), in which 28 fatal cases were collected, pulmonary tuberculosis was found to be a common complicating disease. The following report was deemed especially interesting since it is apparently the first to describe primary carcinoma of the lung as an associated condition.

Case Report

History: J. V., a 41-year-old Hungarian factory-hand, was admitted to the Tuberculosis Ward of the New Haven Hospital, May 11, 1934, complaining of long-standing breathlessness and cough, and a recent disabling pain in the back.

The patient's mother had died at the age of 33 with a protracted "cold in the chest"; his father had met death by accident. Two siblings, as well as the patient's wife and two children, were well. No family history of tuberculosis or of carcinoma was obtainable.

The patient had immigrated in 1911, when he was 18 years old. Five years later he secured employment as a weaver in an asbestos factory, and he continued at this occupation uninterruptedly for 18 years. He had considered his general health good until 1925, when he suffered a febrile illness of sudden onset and associated with pain in the left chest; the diagnosis had been "pneumonia." Although the acute illness subsided within a week, the patient was left with distressing dyspnoea on exertion and a moderately productive cough which prevented his returning to work for five months. X-ray examination of the lungs at this time was reported to have revealed nothing abnormal, and the patient resumed his occupation. His symptoms, however, persisted unabated for the next seven years. At the end of this time which was two years before the present hospitalization, alterations at the asbestos factory led to a great reduction in the amount of atmospheric dust to which the patient was daily exposed and his respiratory symptoms disappeared almost completely.

During the eight months preceding his hospital admission the patient de-

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veloped an insidious, gradually increasing pain of aching character throughout the back. Although the removal of five allegedly bad teeth and the application of heliotherapy to the back were followed by temporary amelioration of the pain, its recurrence with gradually increasing severity soon resulted in the patient's complete incapacity for work.

During the month before admission the dyspnoea, cough and expectoration had returned along with pain of pleural character in the left axilla. The sputum was described as white and heavy, but not foul. The patient had lost 40 lbs. in the last several months.

Physical examination: A lean male of sallow complexion with anxious, careworn expression. He looked chronically ill and his loose skin suggested that weight loss had been considerable. The patient's movements in bed were cautious and deliberate, apparently to avoid pain.

The respirations were regular, 30 per minute, and notably shallow. The lips were cyanotic. A frequent, loose cough "raised" thick, yellowish and blood-streaked sputum in abundance. Dirty teeth, a lightly coated tongue, and injected tonsils were observed incidentally. The chest, with barely perceptible respiratory movements, was definitely asymmetrical, with the left side flatter and less mobile than the right. No measurable diaphragmatic excursion could be demonstrated. Both sides of the chest were dull over the lower lobes, and numerous crepitant and medium moist râles were scattered from scapular angles to bases. The heart did not appear displaced or enlarged and, except for tachycardia of 110 beats per minute, no abnormal signs were noted.

A firm, subcutaneous nodule, about 1 cm. in diameter, was found in the left flank. Movement and manipulation of the lower spine and flexion of the thighs caused agonizing pain in the back with radiation down the thighs. The extremities were remarkable only for moderate clubbing of the fingers with double curvature of the nails, and the nail-beds were cyanotic. The hands, though calloused, presented no "asbestos corns."

Laboratory studies: The red blood cell count was 5,400,000, with 92 per cent haemoglobin; the leucocytes, 13,550, of which 89 per cent were polymorphonuclears. No tubercle bacilli were found in any of the 6 specimens of sputum examined. The urine was normal, and Kahn test of the blood negative. Because of extensive bone disease seen by X-ray, chemical examination of the blood was incidentally carried out, with the following results: The serum's calcium content was 9.27 mgm. per cent, and the phosphorus 4.05 mgm. per cent, with a total protein level of 6.14 per cent, of which 3.19 per cent and 2.45 per cent were made up of albumen and globulin respectively. The icteric index was 4.

Stereoradiographic examination of the chest revealed a narrowing of the posterior intercostal spaces in the lower left hemithorax. The tracheal, mediastinal and cardiac shadows were normal in character and position, but the hilar shadows on both sides were increased in size and density. The bronchovascular markings throughout both lung-fields were obscured by a coarse, rather dense, nodular infiltration, which roughly followed the course of the linear markings and was symmetrically distributed throughout both entire lung-fields. In the left lower lobe was an associated haziness, with a poorly defined area of complete opacity between the left heart border and lateral chest-wall. The latter change suggested partial atelectasis or a pneumonic process in the left lower lobe. In view of the additional discovery of widespread destructive bone lesions of the pelvis and lumbar spine, which were characteristic of metastatic carcinoma, the pulmonary findings were summarized as pneumonoconiosis and additional infiltration of the left lower lobe due probably to a malignant bronchogenic tumor.

Course: Throughout the ten days of hospitalization there was fever ranging continuously between 100° and 103°F., with the heart rate varying between 100 and 130. The patient complained repeatedly of distressing pains in the back and thighs, and analgesics had to be administered liberally. A steady and profuse perspiration sometimes required several changes of clothing daily. After a few days, patchy signs of pulmonary consolidation and pleurisy appeared over the lower lobe of the left lung; with this, the cyanosis grew deeper and the dyspnoea became so extreme that the patient found it difficult to take his meals. A loose cough produced bloody sputum in moderate amounts. On the last day, after a series of particularly violent coughing spells, the patient's pulse suddenly weakened, the skin grew clammy, and he complained of a smothering sensation in his chest. In spite of stimulating measures, including adrenalin and caffein hypodermically, death ensued within a few minutes of the onset of collapse.

Necropsy: The report of the necropsy findings will be limited to the pertinent changes in the lungs. Both pleural cavities were completely obliterated by firm fibrous adhesions. The lungs, after removal from the body, retained almost the shape which they had while *in situ*. With the parietal pleura and part of the adherent diaphragm attached, the right lung weighed 1,179 and the left 1,128 gm. They were both fairly noncrepitant and of a rubbery firmness which rendered sectioning unusually easy. The grayish-red surfaces, which were mottled with large amounts of black pigment, revealed a large, solid tumor in the periphery of the lower lobe of the left lung (figure 1). The mass measured approximately 5 x 5 x 4 cm., its edges were well demarcated, and it was light gray with mottled zones of black pigmentation. A few tumor nodules,

about 1 cm. in diameter, were scattered through the remainder of the lungs and had a mucinous appearance on section. At the hilum of the left lung was a large, firm lymph node measuring 2 x 1.5 x 1 cm., which revealed about half

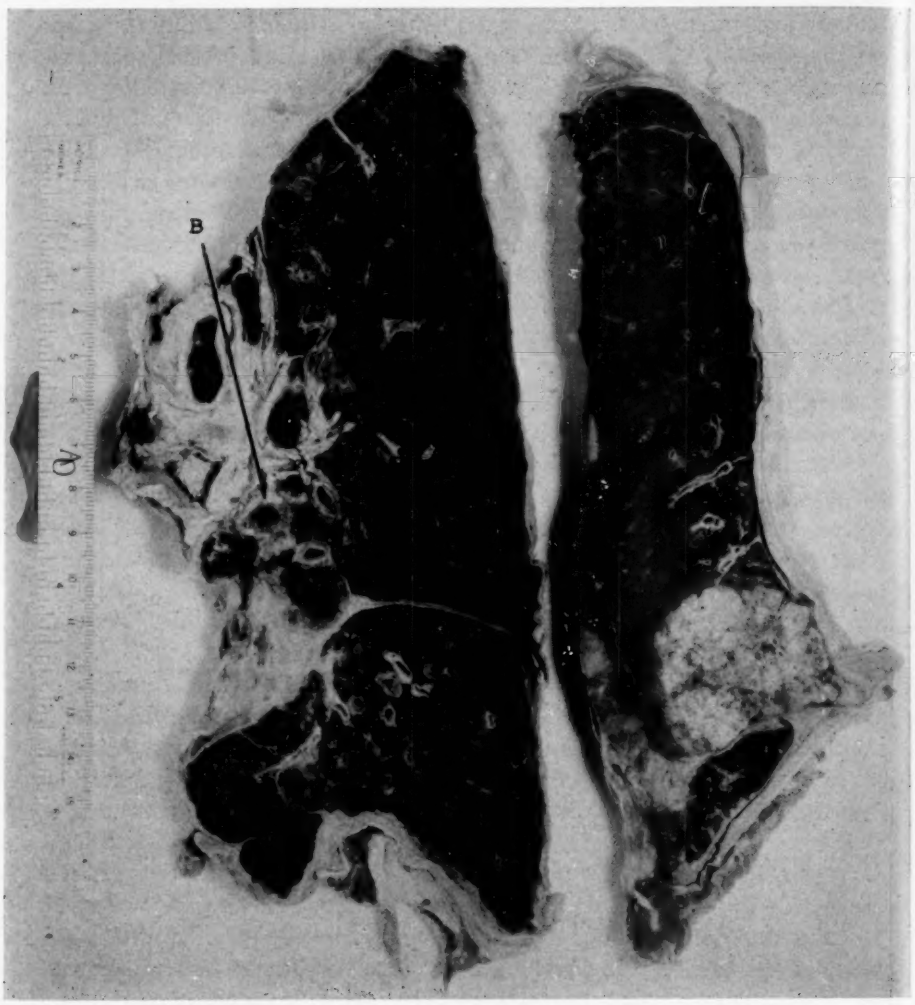

Fig. 1. Pulmonary asbestosis with bronchogenic carcinoma: B, primary site in main bronchus of left lower lobe. Photomicrograph of this region is shown in figure 2.

its substance to be occupied by tumor metastasis. A lymph node of similar dimensions was present at the hilum of the right lung, but it contained no tumor. Careful examinations of the bronchi revealed the primary site of the tumor to

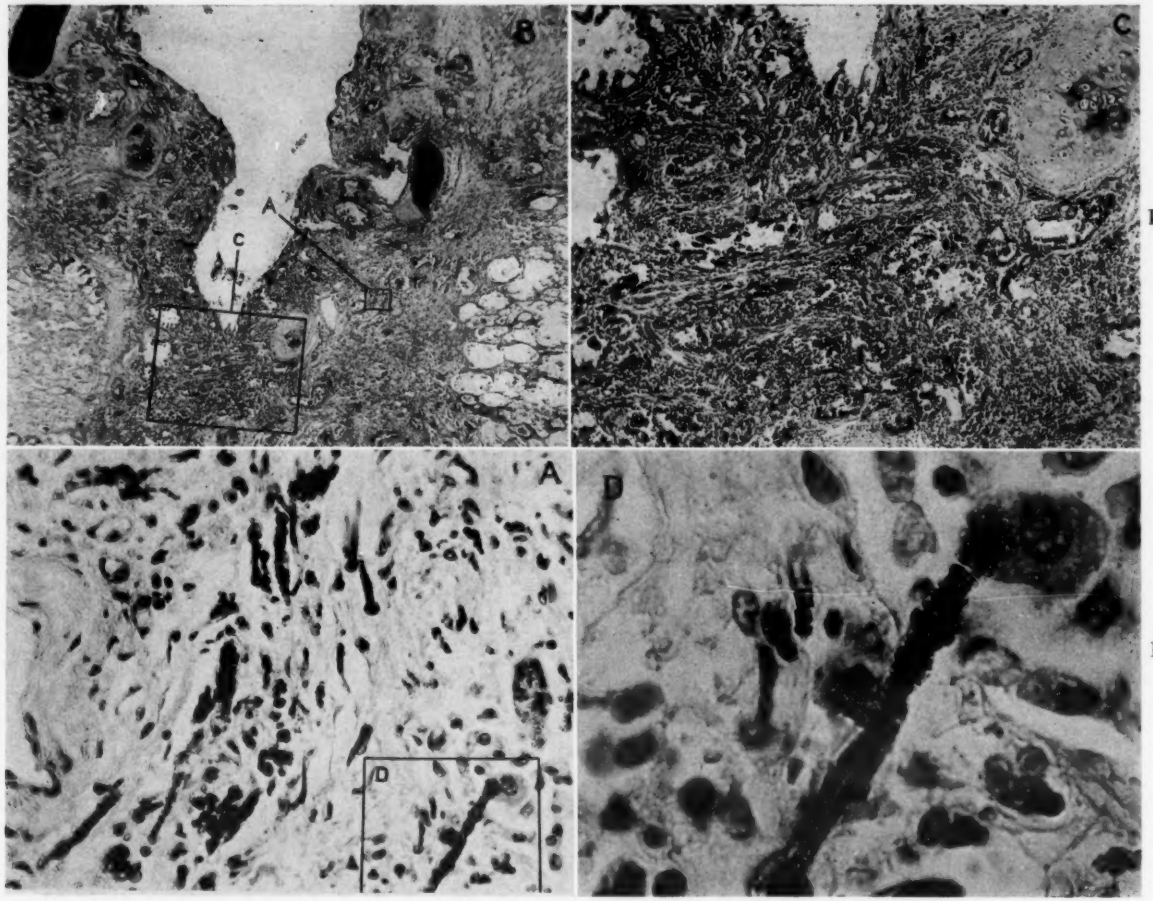

Fig. 2

Fig. 3

Fig. 4

Fig. 5

Fig. 2. Carcinoma of bronchus in figure 1: C, area shown in figure 3; A, area shown in figure 4. ×12.
Fig. 3. Carcinoma of bronchus probably arising from submucosal glands, area C in figure 2. ×40.
Fig. 4. Asbestosis bodies, area A in figure 2: D, asbestosis body shown in figure 5. ×250.
Fig. 5. Asbestosis body, area D in figure 4. ×666

be in a large branch of the main bronchus of the left lower lobe (see B, figure 1). At this point the mucosal surface was roughened and finely nodular; the bronchial wall was thickened and infiltrated by firm, grayish tumor tissue. The bronchus itself led directly into the large tumor mass described in the left lower lobe.

Miscroscopic examination of fresh fluid scraped from the cut lung surfaces showed large numbers of typical asbestosis bodies.

Histological sections confirmed the primary site of the tumor in the bronchus of the lower lobe of the left lung (figure 2). Here in the submucosa and in a considerable zone of the peribronchial tissue were groups of carcinoma cells arranged in well-formed acinous structures which varied greatly in size and shape (figure 3). The neoplastic cells lining the acini were one to several layers in thickness. They were almost all hyperchromatic, varied considerably in size and shape, and exhibited very few mitotic figures. The arrangement and appearance of these cells were quite similar to those of submucosal bronchial glands. There was a tendency for the nuclei to be located at the base of the cells similar to their position in normal submucosal glands. Many of the carcinomatous acini were filled with a pale, gray-staining mucinous material, and in some of the preparations of the bronchus apparently normal submucosal glands could be seen merging with carcinomatous growth.

Asbestosis bodies were scattered throughout the pulmonary parenchyma, in alveoli for the most part and also extending through the carcinomatous zones (figure 4). The color of these bodies was yellowish-brown to brownish-black. They had varying shapes, but tended to be in the form of nodular rods with enlarged rounded heads. In many of the bodies a central somewhat paler and translucent core apparently represented the original asbestos fibre (figure 5). These asbestosis bodies did not give a positive iron reaction. In many instances they were enclosed in the cytoplasm of the macrophages, which were very numerous in the alveoli. Many of the macrophages were multinucleated and extremely large.

There was some diffuse, fibrous thickening of the alveolar walls, and the regions around the bronchi and bronchioles contained a large amount of fibrous tissue. The pleura in all the preparations was thickened, dense and hyalinized.

Tumor metastases, besides those in the lungs and tracheobronchial lymph nodes, were also present in the aortic lymph nodes, the right adrenal gland, the left external oblique abdominal muscle, and in the bony pelvis, vertebrae and skull.

DISCUSSION

Pulmonary asbestosis, a form of pneumonoconiosis which is growing in medical and industrial importance, has been fully discussed in a

recent review by Gloyne (2). Clinically, the condition is characterized chiefly by dyspnoea, by the appearance of a fine, diffuse fibrosis, and by asbestosis bodies demonstrable in the sputum. A review of the fatal cases reported in the literature up to 1932 (1) indicates that the condition comes on slowly and requires an average of 9 years of exposure to the dust before the onset of symptoms. The total time of exposure in uncomplicated cases with fatal terminations was found to average 16 years. Pathologically, the pulmonary fibrosis is diffuse and is most marked around bronchioles and bronchi. This is in distinction to the fibrosis of silicosis, which consists of discrete, dense, hyalinized connective-tissue nodules around and in the pulmonary lymphoid tissue. Asbestosis bodies are always demonstrable in the microscopic sections.

The association between the pulmonary asbestosis and carcinoma in this case is unique and the possible interrelationship of the two processes offers interesting speculation. Gloyne (2) mentions one case of pulmonary asbestosis with carcinoma of the pleura and adds, "There is no evidence at the moment that this is in any way related to the asbestosis." Otherwise, no mention of any such associated pulmonary malignant tumor has been found in the literature.

The relationship between exposure to irritating dusts and malignancy of the lung has aroused a great deal of comment, especially since various statistics would tend to show that the incidence of pulmonary cancer is increasing. Recently, Hruby and Sweany (3) have analyzed the incidence of cancer of the lung and they conclude that not only has there been an approximately tenfold increase in the number of cases coming to autopsy within the last forty years, but that a twofold increase has occurred in the last ten years alone.

Reports of other forms of pneumonoconiosis in which carcinoma of the lung has occurred are fairly numerous. It is not uncommon in silicosis (4). The incidence (10 per cent) of carcinoma of the lung found at autopsy among the cobalt miners in Schneeberg is well known (5).

That the irritating effects of the inhaled asbestos particles may in this case have been a significant factor concerned in the development of the primary lung cancer seems sufficiently plausible to be worthy of consideration.

SUMMARY

1. The clinical and anatomical findings are presented in a case of pulmonary asbestosis with an associated primary carcinoma of the lung.

2. The associated incidence and possible aetiological relationships of pneumonoconiosis to carcinoma of the lung are discussed.

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AGRANULOCYTIC ANGINA FOLLOWING SANOCRYSIN[1]

A Case Report

SPENCER SCHWARTZ AND F. H. HEISE

Case no. 9112: Miss L. B. M., a 23-year-old, white, telephone operator, of Italian ancestry, was admitted February 16, 1934.

None of her family had ever had tuberculosis, nor had she any knowledge of exposure to it.

Her general health had been good. She had contracted measles and mumps as a child, gonorrhoea at the age of 18 which subsided promptly under treatment, and tonsillitis four years ago followed by tonsillectomy under ether anaesthesia.

Her present illness began October 1, 1933, with a cold and cough that persisted until November 23, 1933, at which time she was forced to stop work because of the onset of fever (101°–105°F.), chills, bilateral pain in the chest and increase in cough and expectoration. A diagnosis of pneumonia was made by her physician. In January, 1934, pulmonary tuberculosis was diagnosed by X-ray examination. The patient rested at home, enjoying a moderate abatement of symptoms until admission.

General physical examination was negative except for enlarged, but not tender left cerivical and left axillary lymph nodes.

Examination of chest: On the right, impaired percussion to 3rd rib and 6th vertebral spine; bronchovesicular breathing to 2nd rib and 4th vertebral spine; vocal resonance increased to the 2nd rib and 5th vertebral spine; and moderately coarse râles to 3rd rib; on the left no definite abnormalities.

X-ray examination: Dense mottling throughout the upper two-thirds of the right lung, with deviation of the trachea to that side, (a definite increase when compared with her earlier films) and on the left a small amount of mottling in the apex.

The temperature ranged from 98° to 102°F. and the pulse from 70 to 110. The sputum was mucoid, and positive (Gaffky III); the urine was negative; and the blood sedimentation 28 mm. per hour (Cutler). X-ray examination of the intestinal tract was negative.

Diagnosis: Pulmonary tuberculosis, moderately advanced B.

Artificial pneumothorax was attempted without success, March 7, 1934; and temporary interruption of the right phrenic nerve, March 15, 1934. Following this the patient's temperature dropped to 99.5°F. or below for about

[1] From the Trudeau Sanatorium, Trudeau, New York.

two weeks. However, April 1, it again rose and continued at 102° to 103.5°F. Throughout this time the patient remained bright and cheerful and had few complaints. However, both X-ray and physical signs indicated that the process in the right lung was advancing.

Sanocrysin treatment was begun April 18, 1934, and stopped June 6, 1934; the doses were, April 18, 0.01 gm.; April 25, 0.01 gm.; April 28, 0.025 gm.; May 5, 0.05 gm.; May 9, 0.1 gm.; May 16, 0.15 gm.; May 23, 0.20 gm.; June 6, 0.25 gm.; a total of 0.795 gm. injected. The urine was examined weekly or oftener during this period, and a trace of albumin noted on only one occasion. No discernible reactions occurred. The temperature ranged from 101° to 102°F. during the first two weeks of treatment and from 100° to 101° during the rest of the period. Other medication between April 18 and June 10 consisted of an ounce of mineral oil daily, a total of 0.25 to 0.5 grain of codeine sulphate daily, one 1.5 grain amytal tablet April 18 and April 24, and one capsule containing caffeine gr. 1, acetanilid gr. 2, and phenacetine gr. 3, on April 24 and May 24.

On June 10, the patient complained of sore throat. On examination marked redness and slight oedema of the pharynx and larynx were seen. This continued, and by June 15 oedema of the epiglottis had increased to such a point that the patient experienced great difficulty in swallowing, as well as moderate difficulty in breathing. White membranous patches, the removal of which left a bleeding surface, were in the tonsillar fossae. Later this membrane increased and extended into the larynx. The cervical lymph nodes were enlarged and tender. On June 8 the temperature was 99.6°F., and, steadily rising until June 18, 106.4°F. was reached. Subsequently the range was from 104° to

Laboratory Examinations

DATE	R.B.C.	HBG.	INDEX	W.B.C.	POLY.	MONO.	LYM.	EOS.	BAS.	MYEL.
1934		*per cent*			*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
May 7.....	4,000,460	65	0.7	11,900	76	6	16	2	0	0
June 3.....	4,500,000	72	0.8	8,800	69	12	18	1	0	0
June 16.....	3,420,000	54	0.8	400	0	0	100	0	0	0
June 17.....				600	0	0	90	0	0	10
June 17.....				1,300	0	0	88	0	0	12
June 18.....				650	0	0	90	0	0	10
June 19.....				550	0	0	92	0	0	8
June 20.....				700	6	23	64	Metamyelocytes per cent		7

Blood culture: June 16, 1934: Positive for pneumococcus (type III).

Blood culture: June 18, 1934: Positive for pneumococcus (type III).

Throat culture: June 14, 1934: Negative for Vincent's and Klebs-Loeffler bacilli. Few nonhaemolytic streptococci, and many gram-positive cocci.

Membranes from throat: June 16, 1934: Many gram-negative and positive cocci. Few gram-negative rods. Few gram-positive diplococci.

105° until death occurred on June 20. A leucocyte count, June 16, showed a complete absence of polymorphoneuclear cells. A blood culture taken on the same day showed pneumococci (type III).

Diagnosis: Agranulocytic angina, complicated by pneumococcus septicaemia and pulmonary tuberculosis.

Treatment, in addition to local and supporting, consisted of liver-extract by mouth and intramuscularly, pentaneucleotide, and X-ray radiation over the long bones.

COMMENT

A search of the American literature fails to reveal the occurrence of agranulocytic angina following the use of sanocrysin, probably because sanocrysin has been so little used in America. The British and Germans, and particularly the French, have reported several such cases.

Regarding the aetiology in this particular case, while the possibility of the fulminating type of pulmonary tuberculosis as an inciting factor must be considered (13), it seems more reasonable to place the blame upon the sanocrysin. This conception is borne out by the fact that agranulocytic angina has occurred in quiescent and in apparently arrested cases of pulmonary tuberculosis following treatment with gold salts (5) (7), in a case of lupus erythematosus treated with gold- and sodium-thiosulphate (14), and in a rheumatic patient treated with solganol B (auro-thio-glucose; gold 50 per cent (12)).

Agranulocytic angina occurs most commonly in women (1) (15), and at a frequency of about once in a thousand cases treated by gold salts (1).

The amount of gold salt injected seems to have little influence upon either incidence or prognosis; fatal cases having occurred following the use of as little as a total of 0.02 gm. (1). Also, consideration of impurities or substances other than gold present in the injected material seems futile, inasmuch as agranulocytic angina has occurred following the use of four different preparations of this drug (7) (12) (14). Although gold preparations differ chemically from the various barbital and other benzene-ring derivatives[2] (10), there is a similarity of action, both as to the varying dosage necessary to bring on an attack, and as to the relatively small number of people susceptible to this action.

The prognosis is particularly grave in agranulocytic angina following

[2] It may be mentioned that, although it is hardly longer than eighteen months since the first reports of agranulocytosis following pyramidon appeared in American medical literature, such sequelae are being published more and more frequently. A striking feature is the great variability (as respects dosage) of tolerance on the part of the patients.

the use of gold salts (1) (5) (7) (8). It is correspondingly better in neutropoenias demonstrating only partial loss of the polymorphoneuclear cells and little or no angina (1) (3). The presence of a rise in the number of eosinophiles soon after the beginning of treatment is considered by some writers to be a favorable sign (3) (12), and by others to be of no significance (1).

Some of the therapeutic agents that have been used with good effect at one time or another include X-ray irradiation (9) (11) (18), blood-transfusion (4) (6) (16), injections of milk (6) and other foreign proteins (1) (6), intravenous dextrose (19), injections of whole blood intramuscularly (19), a mixture of extracts of bone-marrow, spleen, thymus, hypophysis, and blood-serum of a young goat (18), a silver salvarsan (18), neosalvarsan (18), a normal horse-serum (18), pentonucleotide (2) (14), solganol-A (35 per cent gold in aromatic combination) (12) (16), leucocytic cream (17), the apparently similar aseptic pus (12), sodium nucleinate (12), liver-extract and raw liver (8). The value of solganol and the arsenicals is doubtful, the more logical procedure being to stimulate the bone marrow toward increased production of the missing blood elements, and to supply them from extraneous sources.

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RESULTS OF THE SANOCRYSIN TREATMENT OF TUBERCULOSIS

FRANK I. TERRILL[1]

Following the introduction of intravenous gold (sanocrysin) as a therapeutic agent in the treatment of tuberculosis, by Møllgaard of Denmark, in 1928, a wave of overenthusiasm swept both Europe and the United States. This was soon followed by a flood of articles in the various medical journals of this country condemning gold, and reporting many incidents of therapeutic accidents following its use, principally the occurrence of a heavy metal nephritis. These reports caused almost a cessation of its use in this country.

Curiously enough, the first wave of overuse in Europe was followed by a great reduction; still, in a fair proportion of selected cases its use was continued and to-day we find it being given with benefit in almost every large European clinic.

After using the soluble gold-sodium-thio-sulphate in a group of 41 cases, it is felt that the early bad results were caused by the injection of too large a dose. It is true that this was soon realized by those administering treatment, and the dosage was reduced, but still it seemed that too large an amount was being given. In the series of cases to be reported the maximum used was 500 mgm., in comparison with the maximum of 1 gm. which is customarily given.

While it has been practically impossible to demonstrate in the experimental laboratory the action of gold on the tubercle, it is generally believed that an alteration takes place in the permeability of the cells surrounding it. Certainly the action is not that of a bactericide.

So many factors enter into the clinical course followed by a tuberculosis patient that it is extremely difficult to judge the value of an isolated procedure. All patients treated were under strict sanatorium care, and we know that many cases so treated eventually recover without specific treatment, other than rest. The patients chosen for intravenous gold had all been under treatment for a year or more, without making satisfactory progress, so that the improvements and arrests that resulted must be in some measure due to the additional treatment.

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Of the 41 cases, all were moderately advanced or far advanced, the majority (30) falling by far into the latter class. While no adequate controls were observed, except that none had shown improvement under the usual care, still the results were quite conclusive as to the value of the drug in selected cases.

The results in 41 cases after eighteen months of treatment were as follows:

1:

Clinically improved	18	Not improved	10
Markedly improved	10	Adverse results	3

2: A gain in weight of over 5 lbs. occurred in 16 patients during a three-months period following initial treatment.

3: Roentgenogram improvement to a perceptible degree was manifested in 15 cases. Cavity-closure occurred in 10 cases, in all of which cavities were of the thin-walled type, and no larger than 4 cm. in diameter.

4: Diminished amounts of sputum were present in 19 cases. Probably the best index of determination of the value of any tuberculosis treatment is the percentage of cases in which a change in the sputum occurs. In this group 10 cases became negative for tubercle bacilli within three months after the beginning of the treatment with gold.

5: Two patients were made definitely worse, a very low tolerance being present and some reaction following each dose, resulting in a spread of the disease to previously uninfected lung.

After eighteen months experience with the drug, several conclusions as to the amount to be used were ascertained. At the start a relatively short course was given, and it was found that several patients improved both in a general way and in the lessening of the amount of sputum while under treatment, but as soon as the gold treatment ceased there was a return of symptoms. In these cases another course was soon started. Now, we are beginning with a very small dose (10 mgm.) and gradually increasing it to 250 mgm. This dose of 250 mgm. is maintained for from five to eight injections before a rapid increase to 500 mgm. is given. Formerly, we increased the amount to 500 mgm. and this dose was repeated from two to six times, depending upon the tolerance of the patient. Recently only two to three injections of the maximum dose were used. The total amount of gold given in a course varied from 3 to 5 gm. It was given at weekly intervals, unless there was some reason for a longer intermission.

Weekly urine analyses were carried out during the course of treatment

and for at least six weeks following its conclusion. In only 2 cases did a slight albuminuria occur, and in both it was of a very transient nature, not making it necessary to cease treatment entirely, but only to increase the time-intervals. Of course, if it is established that a patient has either a very low tolerance or does not react well to the treatment, it should be discontinued as harm can be done by persisting with injections.

CONCLUSIONS

Intravenous gold is of value in the treatment of tuberculosis and has a definite place in the armament of a phthisiotherapist. It is not applicable to all cases, the moderately advanced with relatively small cavities seemingly being the best suited for obtaining good results. In no case should gold therapy be substituted for collapse therapy, even for a trial, as much valuable time might be lost. It is not intended as a basic treatment in tuberculosis, but as a supplementary measure to be used concurrently with rest and collapse measures.

FIG. 1A. Mrs. G., age 32. Roentgenogram taken January 28, 1935. Patient in fair physical condition. Moderate cough with positive sputum. X-ray shows bilateral active disease with a small cavity in the left and in the right subclavicular areas.

FIG. 1B. X-ray of same patient taken May 14, 1935, following a course of intravenous gold, shows disappearance of the two small cavities together with much of the infiltration. Sputum negative; no cough. Weight gain of 32 pounds.

FIG. 2A. Miss F., age 23. Roentgenogram taken January 16, 1935. Patient in poor physical condition. Cough marked, with profuse positive sputum. Large cavity in left apex. Artificial pneumothorax could not be carried out because of pleural adhesions. Course of intravenous gold initiated January 20, 1935.

FIG. 2B. X-ray taken June 21, 1935, shows cavity much diminished in size. Patient much improved. Cough practically absent, sputum still remains positive. An extrapleural thoracoplasty is now being contemplated. This procedure was not possible before a gold course because of patient's poor condition and exudative character of the disease.

FIG. 1A

FIG. 1B

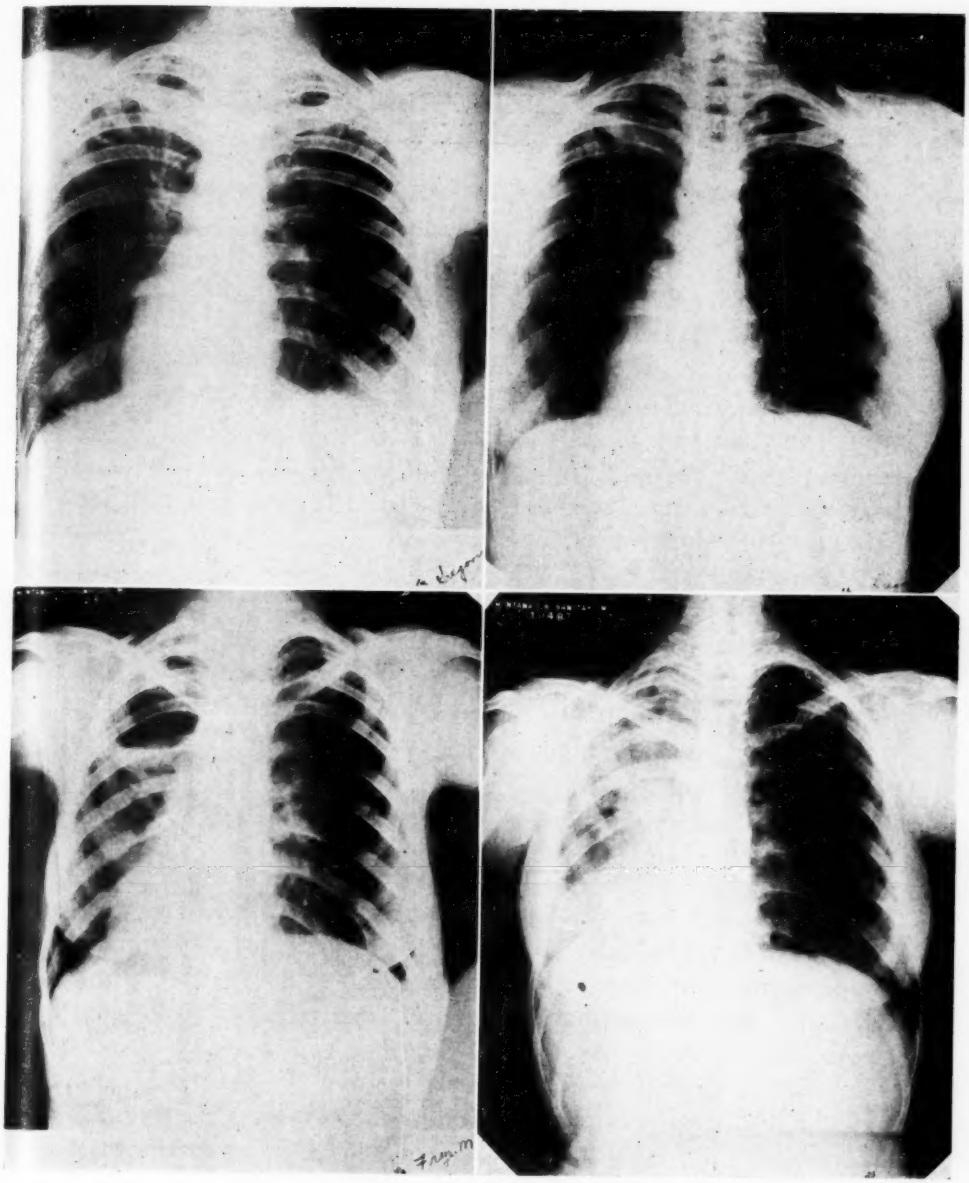

FIG. 2A

FIG. 2B

PLATE 1

ACCIDENTAL PNEUMOPERITONEUM IN ARTIFICIAL-PNEUMOTHORAX THERAPY[1]

C. E. HAMILTON AND PETER AMAZON

Accidental pneumoperitoneum as a complication in artificial pneumothorax is of rare occurrence. This is a report of 2 cases in which this accident occurred following several attempts to find a free pleural space.

In cases apparently suitable for artificial-pneumothorax therapy, on clinical examination and X-ray findings, the presence of a pleural space free from adhesions can be determined only by the needle and the manometer. The occurrence of adhesions between the visceral pleura and the parietal pleura makes it necessary to explore the entire chest surface in the effort to find a free pleural space. It is in this type of a case that one must guard against the possibility of inserting the pneumothorax needle below the diaphragm.

When this occurs, the manometer records an oscillating minus reading which becomes more negative on deep inspiration. These readings are identical with those found in the pleural cavity, and the operator is not aware of the intraperitoneal position of the needle until a subsequent X-ray reveals air below the diaphragm. Occasionally, during the administration of a pneumoperitoneum, the patient will complain of pain in the shoulder. Obliteration of liver dulness is the only physical sign which points to a pneumoperitoneum.

The intraperitoneal pressure in the upper abdomen is similar to that found in the pleural cavity. In the lower abdomen, the intraperitoneal pressure is neutral and gives no manometric oscillations on deep inspiration or expiration. There are many conflicting reports in the literature concerning the intraperitoneal pressure. Hitzenberger (1) observed that the intraperitoneal pressure is increased on inspiration. Suermondt (2) states that normal intraperitoneal pressure is atmospheric. Wagoner (3) found it to be always negative, while Coffey (4) describes it as being always positive. Livingston (5) who has made a clinical study of the abdominal cavity and peritoneum, states that

[1] From the Tuberculosis Service of Kings County Hospital, Brooklyn, New York.

with distinctly thoracic breathing the general intraäbdominal pressure tends to fall during inspiration; with quiet normal breathing (combined abdominal and thoracic type) a fall in pressure within the upper abdomen synchronous with inspiration, is still observed; and it is only with breathing of the abdominal type (thoracic cage remaining relatively quiescent) that the general intra-abdominal pressure shows any tendency to rise during the inspiratory act.

Banyai's (6) extensive experience with pneumoperitoneum is identical with the above.

Pneumoperitoneum has been employed with various degrees of success in intestinal tuberculosis and tuberculous peritonitis. Recently this method has been advocated in conjunction with phrenicectomy for pulmonary collapse in cases with no free pleural space due to adhesions. Figure 1 shows air accidentally introduced into the peritoneum distributed under both domes of the diaphragm. It is therefore difficult to see how such treatment can materially increase the pulmonary collapse on the affected side.

Simon and Abrams (7) reported a similar finding, but did not recognize the pneumoperitoneum and suspected that the air had collected between the diaphragm and the diaphragmatic pleura.

Cases

1: L. E., 26 years of age. Illness, which began five years ago, was arrested after one year of sanatorium care. Present relapse occurred six months ago with fever, cough and expectoration. The physical signs indicated a fibro-ulcerative lesion involving the upper three-fourths of the right lung. After several unsuccessful attempts to find a free pleural space, negative readings were obtained in the eighth interspace in the posterior axillary line. Initial reading was minus 4 to minus 2. Three hundred cubic centimetres of air was administered. Final reading was minus 2 to 0.

X-ray (figure 1) shows a bilateral pneumoperitoneum with most of the air beneath the left dome of the diaphragm. There is no evidence of pneumothorax.

2: F. M., female, 33 years of age. Present illness began four months ago, with pain in the right side of the chest, cough and haemoptysis. The patient has lost 15 lbs. Physical examination reveals signs of consolidation and cavitation of the right upper lobe, with peribronchial infiltration of the right lower lobe. The patient was considered suitable for artificial-pneumothorax therapy. After several unsuccessful attempts to find a free pleural space, negative readings were obtained in the 8th interspace in the anterior axillary line. Initial

reading was minus 4 to 0. Three hundred cubic centimetres of air was administered. Final reading was 0 to plus 2.

X-ray (figure 2) shows a pneumoperitoneum, with a small collection of air beneath the right dome of the diaphragm.

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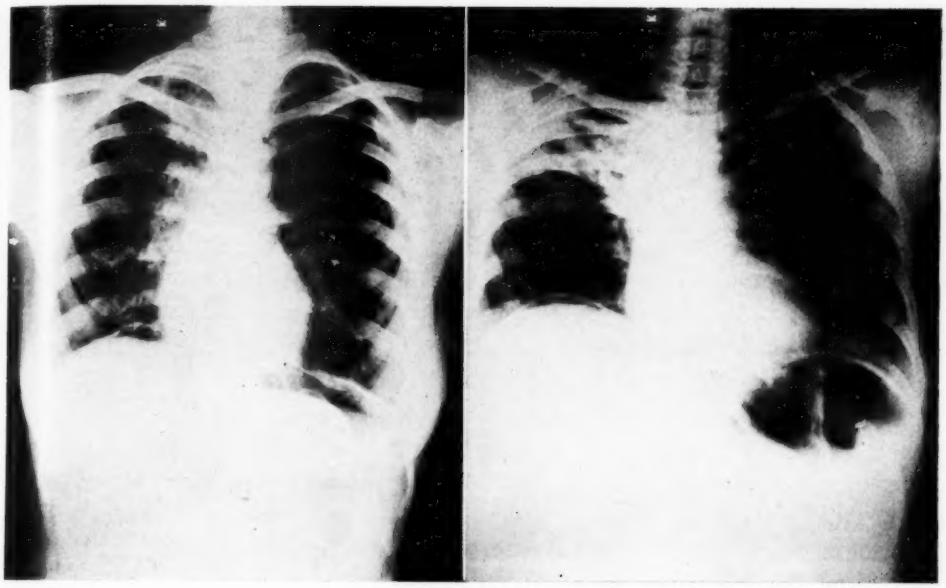

FIG. 1 FIG. 2

PLATE 1

OBSERVATIONS ON THE RED-CELL SEDIMENTATION TEST IN PULMONARY TUBERCULOSIS

H. A. PATTERSON[1]

The sedimentation reaction, which is a nonspecific reaction of citrated blood, is generally regarded as a measure of pathological activity. The result of the sedimentation test taken at the time of admission is helpful in outlining the course of treatment that the patient is to follow, but the subsequent tests are more important. By graphically recording the sedimentation index from time to time, one is able to obtain a fair idea as to the progress of the case. As the test is simple and inexpensive, it can be requested at frequent intervals between routine X-ray examinations. The velocity with which the cells settle is usually considered directly proportional to the extent of pulmonary involvement, being rapid in far-advanced cases and slow in minimal cases. Tappan (1) points out that the velocity is more rapid in cases with positive sputum, loss of weight, rapid pulse, and elevated temperature.

The test cannot be used in diagnosis; but, once a diagnosis has been made, it is of distinct value in estimating the degree of activity. This test is one of the simplest laboratory procedures for determining the presence of a destructive disease. Masten (2) pointed out that, if blood is prevented from coagulating, the red blood corpuscles settle with a different rate in different physiological and pathological conditions. By repeating the test at frequent intervals, one is often able to determine some changes earlier than would be shown by readings of the temperature, pulse, or respiration. In this hospital routine sedimentation tests are run every three months. In some cases, such as following an operation, patients on exercise, or artificial-pneumothorax cases, the sedimentation test is taken at more frequent intervals. The blood is usually taken two hours after breakfast.

The red-cell sedimentation test as described by Cutler (3) has been used at this hospital since November, 1932. Briefly, Cutler's method of red-cell sedimentation may be described as follows: The blood is drawn to the 1-cc. mark in a syringe containing 0.1 cc. of a 3 per cent sodium-

[1] U. S. Marine Hospital, Fort Stanton, New Mexico.

citrate solution. The syringe is gently turned from side to side until its contents have become thoroughly mixed, and is then introduced into a 1-cc. sedimentation tube calibrated to 54 mm. Readings of the level of the red cells are taken every five minutes and recorded graphically. Prior to November, 1932, the Linzenmeier (4) technique was used.

A study of the red-blood sedimentation test has been made on 312 cases at this hospital to determine its relative value. A total of 1,698 sedimentation tests were run. All of the cases with a definite diagnosis

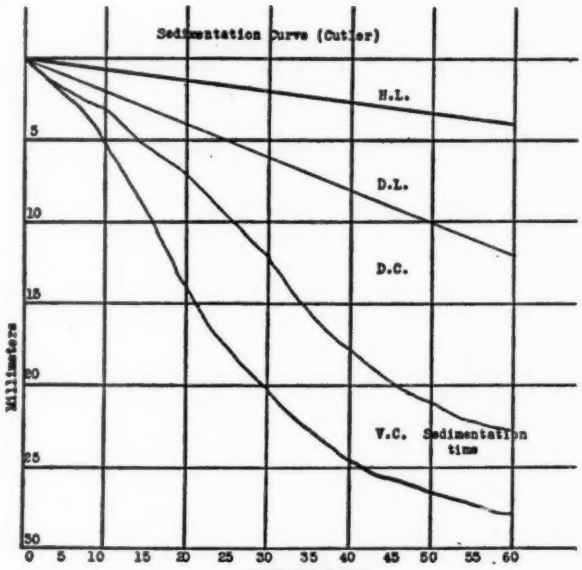

Fig. 1. Sedimentation index and sedimentation time

of pulmonary tuberculosis and the patient who had remained in the hospital long enough to have at least two routine sedimentation tests, were used in this series. All of the patients were adult male seamen, and the diagnosis of pulmonary tuberculosis had been made before they entered this hospital from one of the United States Public Health Service coast hospitals.

The sedimentation index and the sedimentation time are recorded in figure 1 (Cutler). By plotting the fall in red blood cells along the vertical axis against the time in minutes along the horizontal axis the

sedimentation curve is obtained. The curves can be divided into four general groups, as is illustrated by Siltzbach (5), as follows: (a) horizontal line (normal), (b) diagonal line (mild activity), (c) diagonal curve (moderate activity), (d) vertical curve (severe activity).

Results

The average sedimentation index on 20 normal adult male employees at this hospital was 3.5 mm. (table 1). All of these tests were run at

TABLE 1

Red-cell sedimentation index of 20 normal male employees

AGE	GRAPH		SEDIMENTATION INDEX BY CUTLER'S METHOD	SEDIMENTATION INDEX BY LINZENMEIER'S METHOD
	Horizontal line	Diagonal line		
23	plus		1.5	6 hours plus
25	plus		2.5	6 hours plus
22	plus		3.5	6 hours plus
26	plus		4.0	6 hours plus
21	plus		6.0	6 hours plus
27	plus		4.5	6 hours plus
27	plus		3.0	6 hours plus
24	plus		1.0	6 hours plus
25	plus		3.0	6 hours plus
23	plus		6.0	6 hours plus
25	plus		2.0	6 hours plus
19	plus		5.0	6 hours plus
23	plus		5.0	6 hours plus
29	plus		1.0	6 hours plus
29	plus		2.0	6 hours plus
27	plus		7.0	6 hours even
20	plus		6.0	6 hours plus
45	plus		4.0	6 hours plus
21	plus		2.0	6 hours plus
34	plus		1.0	6 hours plus
Average sedimentation.....			3.5	

the same time, and, as the Linzenmeier technique had been used prior to November, 1932, they were also run by this method. The range of sedimentation index was from 1 to 7 mm., which is slightly lower than the average found by Cutler; his normal index for males varied from 2 to 8 mm. There was no appreciable difference in the sedimentation rate noted regarding the age of the normals. The oldest normal was

45 years of age and the youngest 19 years of age, with an average age of 25.7 years.

The 312 cases reported in this series were divided as follows: 180

TABLE 2

Average sedimentation index of 180 hospital cases, using National Association Classification

CLASSIFICATION	NUMBER OF CASES	SURGICAL PROCEDURE					RANGE OF SEDIMENTATION INDEX	AVERAGE SEDIMENTATION INDEX
		Artificial pneumothorax	Phrenic exairesis	Thoracoplasty	Aspiration	Pneumolysis		
1768 (10 cases):*								
A. Active								
B. Quiescent	2				1		2 to 19	8.6
C. Apparently arrested	4						1 to 15	2.5
D. Arrested	4						1 to 13	4.3
1769 (106 cases):*								
A. Active	37	21	16		3	1	1 to 28 in 30 minutes	10.7
B. Quiescent	37	12	9	1	2	4	1 to 19	6.8
C. Apparently arrested	15	2	4		1		1 to 14	5.4
D. Arrested	17		4				1 to 16	3.5
1770 (64 cases):*								
A. Active	48	17	25	4	6	2	3 to 29 in 20 minutes	17.5
B. Quiescent	8	2	2	1			2 to 20 in 35 minutes	4.8
C. Apparently arrested	6	3	4	1			1 to 18	4.7
D. Arrested	2						1 to 13	5.3

* 1768 Tuberculosis, pulmonary, chronic. 1. Incipient.
1769 Tuberculosis, pulmonary, chronic. 2. Moderately advanced.
1770 Tuberculosis, pulmonary, chronic. 3. Far advanced.

As based on National Association classification. *Nomenclature of Diseases and Conditions*, United States Public Health Service, miscellaneous publication no. 16, p. 47, revised 1935.

patients under treatment in the hospital; 110 discharged cases; and 22 fatal cases. Table 2 shows the division of the 180 hospital cases into 3 groups, based on the national association classification. The numbers 1768, 1769, and 1770 conform with the new United States Public Health

Service *Nomenclature of Diseases and Conditions* and are explained under table 2. Each of the 3 groups mentioned above was divided into active, quiescent, apparently arrested and arrested, according to the pathological and clinical picture. The average sedimentation index of the 10 incipient cases (1768) as shown in table 2 is as follows: active (no cases); quiescent, 8.6 mm.; apparently arrested, 2.5 mm.; and arrested, 4.3 mm. The average sedimentation index of the 106 moderately advanced cases (1769) is as follows: active, 10.7 mm.; quiescent, 6.8 mm.; apparently arrested, 5.4 mm.; and arrested, 3.5 mm. The average

TABLE 3

Average sedimentation index of all hospital cases

NUMBER OF CASES	NUMBER OF TESTS	AVERAGE SEDIMENTATION INDEX
85 active cases	539	14.6
47 quiescent cases	263	6.4
25 apparently arrested cases	172	4.9
23 arrested cases	192	3.4
Total	1166	

TABLE 4

Average sedimentation index of 312 cases (180 hospital cases and 132 discharged cases)

CLASSIFICATION	NUMBER OF CASES	AVERAGE SEDIMENTATION INDEX
1768*	25	3.9
1769*	108	7.0
1770*	107	14.1
Total	312	

* Classification explained under table 2.

sedimentation index of the 64 far-advanced cases (1770) is as follows: active, 17.5 mm.; quiescent, 4.8 mm.; apparently arrested, 4.7 mm.; and arrested, 5.3 mm.

The 180 hospital cases were grouped, as shown in table 3, according to active, quiescent, apparently arrested, and arrested cases. There were 85 active cases which gave an average sedimentation index of 14.6 mm. based on 539 tests; the 47 quiescent cases, based on 263 tests, gave an average index of 6.4 mm.; the 25 apparently arrested cases, based on 172 tests, gave an average index of 4.9 mm.; and the 23 ar-

TABLE 5

Average sedimentation index of 110 discharged patients, using National Association Classification

CLASSIFICATION	NUMBER OF CASES	SURGICAL PROCEDURE					RANGE OF SEDIMENTATION INDEX	AVERAGE SEDIMENTATION INDEX
		Artificial pneumothorax	Phrenic exairesis	Thoracoplasty	Aspiration	Pneumolysis		
77 cases discharged at own request against medical advice								
1768 (5 cases):*								
A. Active								
B. Quiescent	4	2	2				3 to 17	3.7
C. Apparently arrested								
D. Arrested	1						4 to 5	4.5
1769 (50 cases):*								
A. Active	41	17	7		2		1 to 23	8.1
B. Quiescent	4	2	2				1 to 7	3.3
C. Apparently arrested	4	1	2				3 to 14	4.4
D. Arrested	1						1 to 2	1.5
1770 (22 cases):*								
A. Active	20	9	4		1		1 to 25 in 20 minutes	11.6
B. Quiescent	1						2 to 3	2.6
C. Apparently arrested	1		1				1 to 5	2.8
D. Arrested								
5 transferred cases								
1769 (4 cases):*								
A. Active	3		1				2 to 23	13.1
D. Arrested	1						2 to 14	5.5
1770 (1 case):*								
A. Active	1		1		1		16 to 20	16.7
28 cases discharged having received maximum benefit of hospitalization								
1768 (10 cases):*								
D. Arrested	10		1				1 to 9	3.1
1769 (17 cases):*								
D. Arrested	17	2	4				1 to 13	3.0
1770 (1 case):*								
D. Arrested	1						1 to 3	1.7

* Classification explained under table 2.

rested cases gave an average index of 3.4 mm., as based on 192 tests.

Table 4 shows the average sedimentation of the 312 cases according to the classification. The incipient cases (1768) gave an index of 3.9 mm.; the moderately advanced cases (1769), 7.0 mm.; and the far-advanced cases (1770) gave an index of 14.1 mm.

Table 5 shows the average sedimentation index of the 110 discharged cases. These cases were divided into 3 groups. Of the 110 cases

TABLE 6

Classification and primary cause of death in 22 cases

CLASSIFICATION	PRIMARY CAUSE OF DEATH	NUMBER OF CASES	SURGICAL PROCEDURE					RANGE OF SEDIMENTATION INDEX	AVERAGE SEDIMENTATION INDEX
			Artificial pneumothorax	Phrenic exairesis	Thoracoplasty	Aspiration	Pneumolysis		
1769*	Following thoracoplasty	1		1	1			12 to 18	14.3
	Lobar pneumonia	1						19 to 23 in 25 minutes	23.0
	Nephritis	1						10 to 17	13.7
1770*	Following spontaneous collapse	2						1 to 18	11.2
	Carcinoma of oesophagus	1						14 to 24	19.7
	Tuberculosis, pulmonary	16	7	4		1		3 to 27 in 30 minutes	19.1

Average sedimentation on 22 fatal cases (100 tests) was 17.3

* Classification explained under table 2.

(table 5), 77 had asked for their discharge, the discharge being given at own request against medical advice. The average sedimentation index of these cases is as follows: 5 incipient cases (1768): active (no cases); quiescent, 3.7 mm.; apparently arrested (no cases); and arrested 4.5 mm. Fifty moderately advanced cases (1769): active, 8.1 mm.; quiescent, 3.3 mm.; apparently arrested, 4.4 mm.; and arrested, 1.5 mm. Twenty-two far-advanced cases (1770): active cases, 11.6 mm.; quiescent cases, 2.6 mm.; and apparently arrested cases, 2.8 mm. The average sedimentation index of 5 cases which were transferred was as

follows: 4 moderately advanced cases (1769), divided into active and arrested, had indexes of 13.1 mm. and 5.5 mm., respectively. There was one far-advanced active case (1770) in this group with an average index of 16.7 mm.

Included in the series of 110 discharged cases were 28 arrested cases. The average index of the 10 cases having a diagnosis of incipient pulmonary tuberculosis (1768) was 3.1 mm., while the average index of

TABLE 7

Average sedimentation index of 110 discharged cases and average sedimentation index on 22 fatal cases

NUMBER OF CASES	NUMBER OF TESTS	AVERAGE SEDIMENTATION INDEX
65 active cases	256	9.5
9 quiescent cases	31	3.1
5 apparently arrested cases	21	5.3
31 arrested cases	124	3.1
22 fatal cases	100	17.3
Total	532	

TABLE 8

Average sedimentation index of 110 discharged cases and 180 hospital cases

NUMBER OF CASES	NUMBER OF TESTS	AVERAGE SEDIMENTATION INDEX
150 active cases	795	12.9
56 quiescent cases	294	6.0
30 apparently arrested cases	193	4.9
54 arrested cases	316	3.2

the 17 moderately advanced cases (1769) was 3.0 mm., and the average index of the one far-advanced case (1770) was 1.7 mm.

In this series of 312 cases there were 22 fatal cases. In table 6 is shown the average sedimentation index of the 3 groups, with the primary cause of death in each case. The average index on all of these cases as based on 100 tests was 17.3 mm.

In table 7 is shown a comparison of the average sedimentation rate for the 110 discharged patients with the rate for the 22 fatal cases. The 65 active cases gave an average rate of 9.5 mm. on 256 tests; the 9 quiescent cases gave an average rate of 3.1 mm. on 31 tests; the 5

apparently arrested cases gave an average rate of 5.3 mm. on 21 tests; while the 31 arrested cases gave an average index of 3.1 mm. on 124 tests.

Table 8 shows the average sedimentation rate on the 110 discharged cases and the 180 hospital cases. Of this total of 290 cases the average rates were as follows: 150 active cases gave an average index of 12.9 mm. on 795 tests; 56 quiescent cases gave an average index of 6.0 mm. on 294 tests; 30 apparently arrested cases gave an average index of 4.9 mm. on 193 tests; and 54 arrested cases gave an average rate of 3.2 mm. on 316 tests.

DISCUSSION

The average sedimentation index taken at this hospital was considerably lower than that found by Cutler. The normal index, as based on a study of 20 adult males, was 3.5 mm., the range being between 1 and 7 mm. The active cases (795 tests) gave an index of 12.9 mm.: the quiescent cases (294 tests) gave an index of 6.0 mm.; the apparently arrested cases (193 tests) one of 4.9 mm.; and the arrested cases (316 tests) 3.2 mm. These check with the average mentioned above. The apparently arrested and arrested cases, 4.9 and 3.2 mm., respectively, were well within normal, while the average index of the quiescent cases was just within the limits.

Roche (6) found that the sedimentation of the red blood cells occurs at a slower rate at higher altitudes. His estimations were carried on at an altitude of 5,000 feet. The altitude at this hospital is 6,231 feet. As the altitude has the effect of diminishing the total mass of blood, there is an apparent increase of the red cells.

The sedimentation index checked with the physical and pathological findings, except in a few cases. The following case illustrates an exception:

No. 1453: Adult white male, aged 26, admitted to hospital April 2, 1927, with history of severe persistent cold and elevated afternoon temperature. Physical examination and X-ray findings showed infiltration, both sides, more marked on left, and large cavity at level of left clavicle. Artificial pneumothorax unsuccessful on left. During stay in hospital had frequent attacks of pleurisy, and, in August, 1929, spontaneous collapse of right lung. Sputum examinations persistently positive. Nine sedimentation tests ranged between 3 and 10 mm., with average of 6.6 mm.; and at time of death, March 21, 1935, sedimentation index was 7 mm.

During the entire time that this patient was being treated, there was a gradual extension of pulmonary involvement, the sputum was positive, and there was a slow but gradual loss of weight and strength. The sedimentation index was always better than would be expected from the extent of pulmonary involvement as shown by repeated physical examinations and X-ray pictures.

The following is another case which gave a better sedimentation index than would be expected from the extent of pulmonary involvement:

No. 1910: Adult white male, aged 36, admitted June 28, 1930, with history of general weakness, productive cough, and continuous fatigue. Had several large haemorrhages, but repeatedly refused surgical treatment. Sputum always positive, and examinations showed gradual extension of involvement. Nine sedimentation tests ranged between 6 and 15 mm., with average index 9.7 mm.; and at time of death, February 14, 1935, sedimentation index was 12 mm.

By comparing the average index of the two cases mentioned above with 17.3 mm., the average for the 22 fatal cases, it is seen that the index of these two patients was always at a better level.

The sedimentation index of the following case did not conform with the clinical picture and X-ray findings:

No. 2104: Adult white male, aged 23, admitted February 21, 1932, with history of persistent cold, productive cough, and gradual loss of weight. Physical examination and X-ray findings showed small infiltration on right, and extensive infiltration with multiple cavity-formation from 4th rib up, on left. Sputum positive on admission. Left phrenicoexairesis, March 3, 1932. Six sedimentation tests ranged between 1 and 5 mm., with average of 2.7 mm.; and at time of discharge, March 1, 1934, index was 1 mm. Course of disease while in hospital that of gradual improvement, and at time of discharge sputum negative. Discharged as quiescent case.

The artificial-pneumothorax cases in this series showed an improvement in the sedimentation index in proportion to the degree of collapse obtained. There were 7 pneumolysis operations in this series. The clinical improvement following these operations was also shown by the sedimentation index.

This study of 312 cases was made to determine the relation of the sedimentation test at this hospital to the extent of pulmonary involvement. It was found that the index coincided with the pathological

involvement in most of the cases. The sedimentation test was found to be helpful in eliciting changes in some cases earlier than would be shown by the temperature, pulse, or respiration. The interpretation of the sedimentation test at any hospital should be based on a comparison made at that location. Because of the value and simplicity of the test, it is advisable that the patient have it repeated from time to time after leaving the hospital.

SUMMARY AND CONCLUSIONS

1. The results of the red-cell sedimentation test in a series of 312 cases are reported. There were 1,698 sedimentation tests taken on 312 cases.

2. In 20 normal individuals the sedimentation index ranged from 1 to 7 mm., with an average of 3.5 mm.

3. The sedimentation rate as a whole was slower than that found at hospitals at a lower altitude. The altitude of this hospital is 6,231 feet.

4. There was a close relation between the sedimentation rate and the extent of pulmonary involvement.

5. The sedimentation rate was not proportional to the extent of pulmonary involvement in all cases reported in this paper.

6. Frequent sedimentation tests are advised after the patient has been discharged from the hospital.

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HYDROGEN-ION CONCENTRATION OF THE BLOOD IN PULMONARY TUBERCULOSIS

E. ROBERT WIESE[1]

The untoward course of cases of pulmonary tuberculosis complicated by an uncontrolled diabetes mellitus has suggested not only the probability of some changes in the blood due to the complicating disease but also the possibility of a lesser but similar change in the blood of cases of pulmonary tuberculosis not thus complicated. Because of the comparative simplicity of the technique the La Motte blood-pH outfit was used to determine the possible changes in the hydrogen-ion concentration of the blood.

The method of Cullen (*Jour. Biol. Chem.*, 1922, lii, 501) with certain modifications in technique by Meyers (*Jour. Biol. Chem.*, 1928, lxxviii, 225) was used. By this method the errors due to loss of carbon dioxide, variations in dilution and temperature, and the Donnan equilibrium are avoided. Cullen's method eliminates the Donnan effect by determining the reaction of the diluted plasma itself, and allows for the protein, salt, dilution and temperature effects by a correction experimentally determined by comparison of colorimetric results with potentiometric data. It depends upon the fact that when phenol-red-indicator solution is added to blood-plasma or -serum diluted with physiological salt solution, the indicator gives a definite shade of yellow or red, the shade depending upon the exact degree of alkalinity of the plasma or serum.

Fifty tests were made on the blood of as many persons; of these, 45 specimens were blood of outspoken cases of pulmonary tuberculosis and 5 were from the blood of apparently normal, healthy persons. The results of the tests are shown in table 1. These were taken at a temperature of 23°C. and corrected to 38°C. according to the formula:

pH 38°C. = *pH at t°C.* (colorimetric) + *0.01* (*t°* − *20°*) − *0.23.* where *pH 38°C.* is the pH of the undiluted plasma at 38°C.; *t°C.* is the temperature at which the reading is taken and *pH at t°C.* (colorimetric) is the actual colorimetric reading. A space in table 1 indicates briefly the physical condition of each person tested.

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TABLE 1

NUMBER	INITIALS OF PATIENTS	READING AT 23°C.	CORRECTED READING (38°C.)	PHYSICAL CONDITION OF PERSONS TESTED
1	E. F.	7.475	7.275	Far advanced, bilateral pulmonary tuberculosis; sputum positive
2	J. A.	7.50	7.30	Moderately advanced, unilateral pulmonary tuberculosis; sputum negative
3	C. P.	7.525	7.325	Far advanced, bilateral pulmonary tuberculosis; sputum negative
4	F. C.	7.525	7.325	Far advanced, bilateral pulmonary tuberculosis; sputum positive
5	J. B.	7.525	7.325	Far advanced, bilateral pulmonary tuberculosis; sputum positive; controlled diabetes mellitus
6	N. B.	7.525	7.325	Moderately advanced, bilateral pulmonary tuberculosis; sputum negative
7	J. E.	7.525	7.325	Far advanced, bilateral pulmonary tuberculosis; sputum positive
8	J. S.	7.525	7.325	Far advanced, bilateral pulmonary tuberculosis; sputum positive; gastrointestinal tuberculosis
9	W. K.	7.525	7.325	Far advanced, bilateral pulmonary tuberculosis; cavitation; sputum positive
10	L. C.	7.525	7.325	Far advanced, bilateral pulmonary tuberculosis; sputum positive; gastrointestinal tuberculosis
11	C. L.	7.55	7.35	Far advanced, bilateral pulmonary tuberculosis; cavitation; sputum positive
12	P. B.	7.55	7.35	Far advanced, bilateral pulmonary tuberculosis; cavitation; sputum positive
13	M. R.	7.55	7.35	Far advanced, bilateral pulmonary tuberculosis; cavitation; sputum positive
14	M. M.	7.55	7.35	Incipient pulmonary tuberculosis; no sputum
15	P. G.	7.55	7.35	Far advanced, bilateral pulmonary tuberculosis; sputum positive
16	I. M.	7.55	7.35	Far advanced, bilateral pulmonary tuberculosis; sputum positive; controlled diabetes mellitus
17	C. R.	7.55	7.35	Far advanced, bilateral pulmonary tuberculosis; cavitation; sputum positive
18	E. C.	7.55	7.35	Far advanced, unilateral pulmonary tuberculosis; sputum negative
19	F. W.	7.55	7.35	Far advanced, bilateral pulmonary tuberculosis; fibroid, chronic; no sputum
20	J. H.	7.55	7.35	Far advanced, bilateral chronic pulmonary tuberculosis; sputum positive
21	S. C.	7.55	7.35	Apparently normal and healthy
22	M. G.	7.55	7.35	Far advanced, bilateral pulmonary tuberculosis; sputum negative.
23	M. G.	7.57	7.37	Far advanced, bilateral pulmonary tuberculosis; cavitation; sputum positive
24	M. S.	7.57	7.37	Far advanced, unilateral pulmonary tuberculosis; sputum positive

TABLE 1—*Concluded*

NUMBER	INITIALS OF PATIENTS	READING AT 23°C.	CORRECTED READING (38°C.)	PHYSICAL CONDITION OF PERSONS TESTED
25	V. Mc.	7.575	7.375	Far advanced, bilateral pulmonary tuberculosis; sputum positive
26	M. S.	7.575	7.375	Far advanced, bilateral pulmonary tuberculosis; sputum positive
27	M. C.	7.575	7.375	Incipient, unilateral pulmonary tuberculosis; no sputum
28	J. C.	7.575	7.375	Far advanced, pulmonary tuberculosis; cavitation; sputum positive
29	F. P.	7.575	7.375	Moderately advanced, bilateral pulmonary tuberculosis; chronic; sputum positive
30	M. M.	7.575	7.375	Moderately advanced, unilateral pulmonary tuberculosis; apparently arrested; no sputum
31	S. C.	7.575	7.375	Far advanced, unilateral pulmonary tuberculosis; cavitation; sputum positive
32	J. J.	7.575	7.375	Moderately advanced, pulmonary tuberculosis; sputum positive
33	G. S.	7.575	7.375	Far advanced, bilateral pulmonary tuberculosis; cavitation; sputum positive
34	H. N.	7.575	7.375	Far advanced, bilateral pulmonary tuberculosis; cavitation; sputum positive
35	H. H.	7.575	7.375	Far advanced, bilateral pulmonary tuberculosis; sputum positive
36	N. P.	7.575	7.375	Far advanced, bilateral pulmonary tuberculosis; sputum positive
37	R. W.	7.575	7.375	Apparently normal and healthy
38	E. W.	7.575	7.375	Apparently normal and healthy
39	B. W.	7.575	7.375	Apparently normal and healthy
40	J. C.	7.575	7.375	Apparently normal and healthy
41	W. W.	7.60	7.40	Far advanced, bilateral pulmonary tuberculosis; sputum negative
42	J. P.	7.60	7.40	Far advanced, bilateral pulmonary tuberculosis; sputum positive; gastrointestinal tuberculosis
43	A. O.	7.60	7.40	Far advanced, bilateral pulmonary tuberculosis; sputum positive
44	E. E.	7.60	7.40	Moderately advanced, unilateral pulmonary tuberculosis; sputum negative
45	L. D.	7.60	7.40	Far advanced, bilateral pulmonary tuberculosis; cavitation; sputum positive
46	W. S.	7.60	7.40	Far advanced, unilateral pulmonary tuberculosis; sputum negative; pneumothorax
47	J. A.	7.60	7.40	Far advanced, bilateral pulmonary tuberculosis; sputum negative
48	P. M.	7.60	7.40	Far advanced, bilateral pulmonary tuberculosis; cavitation; sputum positive
49	D. C.	7.60	7.40	Incipient pulmonary tuberculosis; sputum positive; asthma
50	E. McC.	7.65	7.45	Far advanced, bilateral pulmonary tuberculosis; fibroid; sputum negative

REMARKS AND CONCLUSIONS

Examination of table 1 shows among other things—

1. Only 9 cases (18 per cent) yielded the figure (7.40) usually considered the normal pH index of the blood.

2. There are no extreme variations from that of normal.

3. Such variations correspond in no wise to the physical condition of the patient.

The only logical conclusion seems to be that there is nothing in the hydrogen-ion concentration of the blood of cases of pulmonary tuberculosis that is of diagnostic or prognostic value.

This paper is submitted with the hope that its very lack of any startling evidence may stimulate researches along a similar line.

PULMONARY TUBERCULOSIS AND DIABETES MELLITUS[1]

J. J. WIENER AND JULIUS KAVEE

1. INTRODUCTION

Incidence, Age and Sex-Distribution

The material forming the basis of this presentation is drawn from an analysis of 218 cases, in which tuberculosis and diabetes coexisted, observed at the Montefiore Hospital and its country sanatorium at Bedford Hills during the decade ending December 31, 1932. During this period 3,385 individuals were admitted to the tuberculosis wards at Montefiore Hospital. Among the total admissions, instances in which both diabetes mellitus and pulmonary tuberculosis were present equalled 6.4 per cent. This percentage is higher than the figures published by Landis, Funk and Montgomery (1), Banyai (2), and Wassmund (3), among whose tuberculous patients diabetes was present in one-half to two-thirds of 1 per cent. The much greater frequency with which diabetes was encountered on the wards of Montefiore Hospital may be explained among other factors by the following: The patients were almost exclusively Jewish. Individuals with both diabetes mellitus and pulmonary tuberculosis are sent to this institution not only from Bedford Sanatorium but also from many other hospitals and clinics in the Metropolitan district. Many who are sent to other institutions express a preference for Montefiore Hospital because they have learned that special attention is being given to diabetics on the Tuberculosis Service and because the diet employed at Montefiore Hospital is more compatable with the religion and taste of the orthodox Jew. It is therefore improbable that 6.4 per cent of patients admitted to other tuberculosis institutions or among tuberculous patients in private practice will be found to have diabetes. Thus, we have had an opportunity to study an unusual number of diabetics and to have under our observation at all times between 20 and 30 ward-patients and 25 to 30 out-patients in whom both diseases coexist.

There has been no agreement among the numerous authors who have

[1] From the Tuberculosis Division of the Montefiore Hospital and Country Sanatorium.

studied the question as to whether or not tuberculosis is more frequent in the diabetic than in the nondiabetic. Banyai collected 8,520 cases of diabetes with an incidence of 2.6 per cent of pulmonary tuberculosis, which he took to indicate that pulmonary tuberculosis was three times as frequent among diabetics as compared to nondiabetics. In reviewing the literature Fitz (4) compiled 5,500 cases of diabetes, with an incidence of 1.6 per cent of pulmonary tuberculosis. In studying 500 diabetics, Sevringhaus (5) found four who died of pulmonary tuberculosis and four others who had active tuberculosis, an incidence of 1.6 per cent. Murphy and Moxon (6), in listing the complications among 827 diabetics, found 40 cases of pulmonary tuberculosis, an incidence of 4.8

TABLE 1

Annual incidence of diabetes with tuberculosis at Montefiore Hospital

YEAR	ADMISSIONS TO TUBERCULOSIS SERVICE	DIABETICS ADMITTED		DEATHS IN HOSPITAL			LEFT HOSPITAL ALIVE		
		Male	Female	Total	Male	Female	Total	Male	Female
1923	395	17	7	14	11	3	10	6	4
1924	388	9	12	15	8	7	6	1	5
1925	401	8	13	15	8	7	6	0	6
1926	417	10	10	11	5	6	9	5	4
1927	392	17	9	18	12	6	8	5	3
1928	310	9	12	16	8	8	5	1	4
1929	292	8	7	10	5	5	5	3	2
1930	238	15	7	11	8	3	11	7	4
1931	206	11	3	6	4	2	8	7	1
1932	346	20	14	14	9	5	20	11	9
Total....	3,385	124	94	130	78	52	88	46	42

per cent. During the period of this study, the general hospital population of their institution showed an incidence of pulmonary tuberculosis of 3.2 per cent. Murphy and Moxon, commenting on Sevringhaus's article which appeared at the same time, account for the difference in incidence between their findings and those of Sevringhaus by stating that their patients came from an urban population whereas Sevringhaus's patients were drawn from rural sections. It is well known that pulmonary tuberculosis is more frequent among city dwellers than rural inhabitants. In a total of 701 diabetic patients admitted to Montefiore Hospital to services other than the Tuberculosis Service, five developed pulmonary tuberculosis while under observation at the hospital, an incidence of 0.7 per cent.

However, of the 909 patients admitted to Montefiore Hospital with diabetes, 218 had tuberculosis, an incidence of 23.9 per cent. This figure cannot, of course, be compared with the incidence of tuberculosis in the ordinary sanatorium or general hospital treating diabetics. Our hospital population contains such a large number of tuberculosis patients that no comparisons are justified. The figure of 23.9 per cent of pulmonary tuberculosis occurring in 909 diabetics is closer to the usual percentage found upon postmortem examination of fatal cases of diabetes mellitus (Fitz (4)).

The admissions of tuberculosis patients with diabetes did not vary greatly from year to year, remaining in general constant both in percentage and in number, until 1932 when, because of an intense interest

TABLE 2

Age and sex incidence among patients suffering with diabetes and tuberculosis at Montefiore Hospital

AGE	FEMALES			MALES		
	Number admitted	Per cent of total females	Cumulative per cent	Number admitted	Per cent of total males	Cumulative per cent
years						
1–10	0	0.0	0.0	0	0.0	0.0
11–20	2	2.1	2.1	3	2.4	2.4
21–30	2	2.1	4.2	9	7.3	9.7
31–40	8	8.5	12.7	17	13.7	23.4
41–50	28	29.8	42.5	34	27.5	50.9
51–60	34	36.2	78.7	37	29.8	80.7
61–70	17	18.1	96.8	24	19.3	100.0
71–up	3	3.2	100.0	0	0.0	100.0

in the problem, a far greater number of diabetics than usual were admitted to the Tuberculosis Service. (See table 1.)

The age-incidence of those having both diseases differed in no wise from the expected age-incidence among diabetics in whom tuberculosis was not a factor. (See table 2.) Upon entering the hospital the vast majority of the patients were over forty years of age. Of the entire group of 218 cases only 18.8 per cent were under forty years of age, and 81.2 per cent were over forty years; 32.5 per cent of the total number were in the sixth decade. The average age of all the patients was 54.3 years. This corresponds with the observations of other investigators (Joslin (7), Fitz (4), Wilder and Adams (8), and Banyai (2)). All agree that tuberculosis as a complication of diabetes occurs chiefly in

later life. Very few cases occur before the fortieth year of life or after the seventieth.

Of the 218 patients admitted, 124 were men and 94 were women (table 2). The frequency of diabetes and tuberculosis in women in relation to the number of admissions was 8.3 per cent; in men, 5.5 per cent. Thus, although the actual number of males in the series is greater

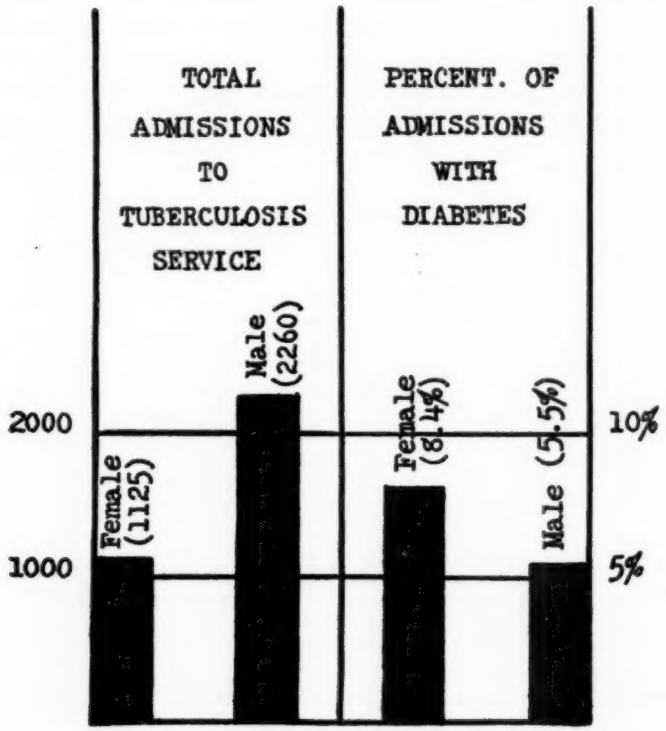

Fig. 1. For discription see text

than that of females (figure 1) the percentage of females in proportion to the total admissions is far greater than the percentage of males.

Of the 218 patients, 45 had a history of tuberculosis among their immediate family, and 36 had a history of diabetes. From among these with a history of either disease, 17, or almost one-half, had a history of both diseases in the immediate family. Thus, 16.5 per cent had a family history of diabetes and 20.6 per cent had a family history of pulmonary tuberculosis. However, it is difficult, if not impossible, to

draw any conclusions from the patient's story of familial disease. Fishberg (9) has ably discussed the futility of attempting to obtain an accurate idea of the effect of family-history upon the development and occurrence of pulmonary tuberculosis. It is doubtful if, with such a widespread disease as pulmonary tuberculosis, any family is free from infection. Very often diabetes mellitus escapes detection by the physician because of its paucity of symptoms. One should therefore be reluctant to draw any conclusion from the foregoing figures as to the familial occurrence of these two diseases.

2. RECIPROCAL RELATIONSHIP BETWEEN THE ONSET OF PULMONARY TUBERCULOSIS AND DIABETES MELLITUS

Those physicians who have written concerning patients in whom these diseases coexisted have been unanimous in one respect: all have reported that, in the vast majority, the diabetes antedates the onset of the pulmonary tuberculosis. In this series of 218 cases, 140, or 64.2 per cent, gave definite evidence of the presence of diabetes mellitus prior to the advent of the pulmonary tuberculosis. This fact lends some weight to the belief that the diabetic is more liable to develop pulmonary tuberculosis than the individual whose carbohydrate metabolism is normal.

In 38 instances, or 17.4 per cent, the pulmonary tuberculosis antedated the onset of diabetes. However, it is worthy of emphasis at this point that in this group the tuberculosis was considered inactive in 29, and in only 9 cases was the pulmonary process active and progressive. This fact is in accord with the findings in the wards of Montefiore Hospital and in other institutions of similar character elsewhere, that glycosuria and diabetes mellitus only rarely develop in the presence of active pulmonary tuberculosis. Thirteen of the 38 patients had had rather prolonged periods of institutional care for their tuberculosis, and the disease had become arrested many years before the discovery of their glycosura. Thirty-five of this group were over thirty-five years of age when the diabetes was discovered. Apparently, therefore, diabetes rarely develops in patients with any form of pulmonary tuberculosis, either fibroid or active, before the age of thirty-five.

Though 25 patients were admitted to the hospital with no symptoms of diabetes mellitus and with a history of very recent onset of their tuberculosis, a careful study of their diabetic status indicated that the diabetes may have been present for a considerable time previous to the

development of the pulmonary process without the patient knowing that the diabetes existed.

In 12 instances the symptoms of both diseases appeared simultaneously and the diagnosis of their presence was likewise made simultaneously. In 3 instances the patients had no pulmonary symptoms and were hospitalized because of their diabetes. In them the tuberculosis was minimal and fibrotic in character and may have been present for some time. Among these it is therefore impossible to state with any degree of certainty which disease appeared first.

Undoubtedly in the overwhelming majority clinical pulmonary tuberculosis occurs as a complication in the obese middle-aged diabetic. However, in a few instances diabetes may occur as a complication in the history of the tuberculous patient, especially when the pulmonary process has become arrested and the patient has reached middle age.

3. MODE OF ONSET OF TUBERCULOSIS IN THE DIABETIC

In discussing the clinical course of the tuberculosis, it is deemed advisable to group the cases according to their mode of onset, development of the complete disease picture, the complications encountered, the therapy applied and the prognosis as judged by mortality figures.[2]

Cough was the most frequent symptom, occurring first in 125 cases. Fever was mentioned as the initial symptom by 34, loss of weight and weakness by twenty-five. Haemoptysis occurred as the initial symptom in 15, or 6.8 per cent, of our group. Drowsiness and coma were noted in eight. Other symptoms such as hoarseness, dyspnoea and diarrhoea occurred rather infrequently.

One hundred and nine cases, or 50 per cent, had a catarrhal type of onset. In this group the tuberculous disease started with mild cough and expectoration. Later, the patients felt weak and noted that they had lost weight and strength, with the entire picture of the beginning

[2] In making this analysis, the difficulties encountered were mainly due to the variations in the patients' response to the pathological changes present. As Libman (10) has recently emphasized in interpretation of pain in disease, the same underlying disease may give rise to subjective manifestations of varying intensity in different individuals depending upon certain unknown factors in the patient's make-up. So it is with other symptoms encountered in these patients; a slight cough would terrify some and others would deny coughing, although they were actually doing so at the time of examination. The presence of fever of a mild degree would prostrate some and others would be continuously at their labor in spite of a constant temperature of 101°F. and make no complaint. Fully realizing the difficulties encountered in classifying symptoms, we felt that it would still be of interest to enumerate the major symptoms in the order of their relative frequency.

of the disease very insidious. These mild symptoms persisted for variable periods of time before a positive diagnosis of tuberculosis was established either by finding tubercle bacilli in the sputum, by definite physical signs, or by fluoroscopic and roentgenographic evidence.

Forty-four cases, or 20.2 per cent, had an active febrile onset. In some the clinical picture appeared to be similar to a pneumonia. In the majority, however, mild to severe grippal symptoms attracted attention to the presence of the pulmonary disease.

Fifteen patients or 6.8 per cent, had a frank haemoptysis as their first indication of any trouble in their lungs.

In 13 cases pleural pain varying from slight discomfort to a severe pleurisy, in two of which an effusion occurred, started the train of symptoms which established the diagnosis.

In 14 instances the onset of the tuberculous disease was completely asymptomatic. Its discovery depended upon the alertness of the examining physician who appreciated that the presence of a silent pulmonary tuberculous infection is often responsible for the difficulty encountered in controlling diabetes mellitus. These diabetics started to lose weight rapidly, became markedly asthenic, or even developed ketosis with no change in their metabolic management. Symptoms and very often definite signs of pulmonary disease were absent and only by roentgen examination could a definite diagnosis of tuberculosis be established. These cases emphasize the absolute necessity for roentgen examination of the chest in any case of diabetes which becomes difficult to control and in which the exact cause of this difficulty cannot be readily established.

4. SYMPTOMS OF TUBERCULOSIS AS THEY OCCUR IN THE DIABETIC

No matter what the type of onset of the tuberculous disease or the clinical course pursued, there are certain features about the symptoms of pulmonary tuberculosis occurring in the diabetic which should be emphasized. Cough was an almost universal complaint; in only 10 instances of the entire series was cough not noted at some time. Emetic cough which interfered seriously with nutrition, insulin dosage and control, occurred only three times, and these three patients were desperately ill, the disease progressing rapidly to a fatal issue.

Pulmonary haemorrhage occurred rather frequently. Haemoptysis of over one ounce, which as a rule recurred several times, took place in 61, or 27.5 per cent, of the 218 cases. When we add to this number

those instances in which streaked sputum was repeatedly found, the total in which bleeding of some type took place becomes 115, or 52.3 per cent.

As reported by Kuthy (11), in 5,872 patients without diabetes 54.3 per cent had haemoptysis. It would appear, therefore, that haemorrhage and haemoptysis in general occurred no more frequently in the diabetic than in nondiabetic tuberculous patients.

Changes in body weight proved to be of unusual interest. In only 33 instances was there no loss of weight prior to admission to the hospital. To emphasize the extremes attained, we have histories recording the loss of 75 lbs. in six months in each of two cases and in others loss of weight of over 100 lbs. over a period of several years. However, the average loss of weight was approximately 50 lbs. within the year preceding admission. Loss of weight, occurring to such a degree in patients who apparently are not extremely toxic from their tuberculosis, is especially noteworthy. Rarely in human disease without a septic toxaemia or in the absence of malignant tumor does one find such a rapid loss of weight as occurs regularly in the tuberculous diabetic. In 25, or 11.4 per cent, of the cases, the diabetes had been well controlled dietetically and with insulin, and, in spite of this fact, a rapid loss of weight and strength developed. There were no definite symptoms or signs suggestive of pulmonary disease as the underlying cause for the break in the metabolic compensation. As a rule physical examination failed to give positive evidence of pulmonary disease. Only by roentgen examination could the disease in the lungs be detected, because in these cases the process is predominantly of the infraclavicular and perihilar exudative types. Therefore too much emphasis cannot be placed on the dictum—*roentgenograph the chest of every diabetic patient who is not progressing favorably in spite of good metabolic management.*

During the patients' stay in the hospital under treatment for both diseases, marked gains in weight for longer or shorter periods were the rule. Patients in the diabetic age-group that were obese prior to the onset of their disease rarely regained their initial weight. Patients in the adolescent age-group gained so much during their hospital stay that often the weight reached a point much above the average normal. This occurred often in spite of a febrile course of the tuberculosis and of progression of the pulmonary process as determined by repeated roentgen examinations.

Fever as a symptom of disease in these cases was not very distressing,

which is not an unusual finding in all cases of tuberculosis. The presence of fever was often undetected by the patient until the thermometer readings became a part of the daily routine.

Anorexia was of very infrequent occurrence. In spite of the presence of the active tuberculosis the usual inordinate desire for food which occurs in diabetics was present. In only 11 cases did loss of appetite present any problem in feeding the patients. However, an exacerbation of the pulmonary disease was often found to be initiated with anorexia. By increasing the amount of insulin given one could often overcome this loss of appetite.

The remainder of the symptoms which occurred in this special group of cases were similar in all respects to the symptoms of pulmonary tuberculosis occurring in the nondiabetic.

5. COURSE OF PULMONARY TUBERCULOSIS IN THE DIABETIC

Tuberculosis, as a disease in middle-aged and aged individuals, usually runs a chronic course with many exacerbations and remissions. During the periods of remission there is comparative freedom from the toxic manifestations of the pulmonary infection. In the diabetic, however, this cyclic course is unusual, and, as a general rule, when pulmonary tuberculosis presents itself the disease progresses steadily to exitus.

In 62.4 per cent of our group of cases the pulmonary tuberculosis progressed without any remissions until death ensued, with the duration of life ranging from two months to six years. In this group the progress of the lesion in the lung was continuous, in some very rapid, in others quite slow. In 20.8 per cent of the 218 cases, the tuberculosis progressed to a fatal issue in less than one year, running an acute toxic course with the daily temperature rising over 102.5°F. These patients had either extensive bronchopneumonic lesions or large isolated areas of consolidation. They were markedly prostrated, and it was impossible to stem the course or abate the symptoms by any means at our command. The following histories are typical of the cases which presented this type of acutely progressive disease:

Case 1: E. F., no. 140–17530, a woman aged sixty, was admitted to the hospital in June, 1929, with a history of having had moderately severe diabetes for several years. Five months before admission she developed a productive cough, with some weakness, and started to lose weight. Two months before entering the hospital she suffered from a pulmonary haemorrhage. Physical and roentgen examination revealed extensive consolidation, multiple small

cavities throughout the left upper lobe, and numerous small areas of infiltration in the left lower lobe. The roentgenogram showed a few tubercles seen in the right upper lobe. The temperature course was hectic, fluctuating between 99.2° and 104.4°F., and the sputum was positive for tubercle bacilli. The diabetes was easily controlled on a high carbohydrate diet with 50 units of insulin daily. However, despite the control of the diabetes, the tuberculosis progressed, and, seven months after the inception of her symptoms, and only one and a half months after admission to the hospital, she died. Postmortem examination revealed extensive tuberculous bronchopneumonia of both lungs, multiple cavitation in the left upper lobe and tuberculosis of the ileum.

Such a rapidly developing bronchopneumonic tuberculosis, while unusual in the aged, is a usual finding in the diabetic.

A similar type of case in the younger age-group is the following:

Case 2: A. S., no. 126–16860, a man, twenty-nine years of age, was admitted to Montefiore Hospital in December, 1928. Diabetes mellitus was first noted in October, 1927, and dietetic treatment was instituted. In June, 1928, the patient began to cough and expectorate, lose weight, and suffer from pulmonary haemorrhages and a febrile course. Six months after the onset of the pulmonary symptoms, he was admitted to Montefiore Hospital. Physical and roentgen examinations revealed extensive infiltrations throughout both lungs, with multilocular cavities in the right upper and the left lower lobes. The diabetes was easily controlled on a high carbohydrate diet with 25 units of insulin daily. However, one month after admission and seven months after the inception of the pulmonary disease, the man died of his tuberculosis. This case likewise illustrates the rapidly fatal course which the tuberculosis pursued.

More often the tuberculosis progressed at a slower rate and the constitutional symptoms were not as marked: For example, the temperature in this larger group rarely rose higher than 101°F. Weakness was always marked, cough and expectoration always present. The patient never was completely free from the intoxication of his tuberculosis, but the distress occasioned by its presence was only moderate. Although losing ground gradually, the patients in this group could be made to gain markedly in weight and strength with a high carbohydrate diet and large amounts of insulin. Those patients who gained weight felt relatively well, even with moderate fever and despite the fact that repeated roentgen examinations revealed a steady progression of the pulmonary tuberculosis. Death, in this group, might be delayed for as long as three years, as illustrated by the following cases:

Case 3: F. B., no. 111–15485, a woman, aged sixty, was admitted to Montefiore Hospital in May, 1926, with a history of having had diabetes mellitus since 1921 which was controlled dietetically. She felt well until September, 1925, when she began to cough, expectorate and lose weight. Physical and roentgen examinations revealed infiltrations from the apex to the ninth rib on the left side, and in the midzone from the 4th to the 8th rib on the right. Her weight on admission was 93½ lbs., and her afternoon temperature was never below 101°F. On a high carbohydrate diet and 20 units of insulin daily she gained 6 lbs. in six weeks. Her febrile course continued and the insulin dosage was raised to 40 units. By August, 1927, she had gained 16 lbs. in weight, despite the steady progression of the pulmonary tuberculosis. Thereafter she refused food and lost weight rapidly, succumbing in December, 1927, two and one-quarter years after the inception of the pulmonary disease. Autopsy revealed an extensive bilateral tuberculosis.

Case 4: J. R., no. 38–12288, a man, aged twenty-two, was admitted to Montefiore Hospital in March, 1924. A simultaneous diagnosis of pulmonary tuberculosis and diabetes mellitus had been made in December, 1923. He had tuberculous infiltrations in the midzone region of both lungs, with a small cavity on the left side. The sputum was positive for tubercle bacilli, and his temperature rose to 101°F. daily. His weight on admission was 120 lbs. and, in spite of fever, he gained rapidly on a high carbohydrate diet and 30 units of insulin daily. Repeated roentgen examinations revealed steady progression of the disease, but he did not lose weight until two weeks before death, which occurred in February, 1925, fifteen months after the symptoms of his pulmonary disease appeared.

The résumé of the histories of these two patients demonstrates that the pulmonary tuberculosis, even though steadily progressing, need not be accompanied by symptoms of overwhelming toxaemia; that, in the presence of advancing disease accompanied by fever, the tuberculous diabetic may gain weight if placed on a high carbohydrate diet, rest and sufficient insulin; and that gain in weight cannot be taken to indicate quiescence, for, in spite of the increase in weight, the patients died of their pulmonary disease.

Although pulmonary tuberculosis in the diabetic usually appears as an exudative process, which continues to progress until the patient dies, there are exceptions. Of the group of 218 cases, in 43 patients, or 17 per cent, the pulmonary lesion either became arrested or had never been clinically active. The nature of the diabetic process played no part in determining the fate of the tuberculous process, for there were a greater

number of severe cases of diabetes in this group than among any of the other groups previously analyzed. Every age-group was represented among these 43 patients, and age appeared to have no bearing upon the future course of the disease. The symptoms of the pulmonary process were not, as a rule, very marked; only 7 patients were febrile on admission, and 6 others occasionally ran a subfebrile temperature for a short period, while the remainder were afebrile throughout their stay. In 3 instances the temperature spontaneously fell to normal within one month after admission. This fact is especially significant when one considers that, in a group of 120 patients who were admitted with a temperature of over 101°F., these 3 were the only ones in whom the temperature subsided spontaneously and did not again rise above normal. In the other 4 patients admitted with fever the pulmonary process became inactive and the course afebrile only after the induction of therapeutic pneumothorax.

Of these 43 patients, 10 have died. The 10 deaths could not be ascribed entirely to the activity of the pulmonary tuberculosis. Three patients suffered a fatal haemoptysis, 2 died as a result of arteriosclerotic heart disease, and in 5 death resulted from a combination of the tuberculosis and degenerative arterial disease.

An analysis of the fate of the 218 patients demonstrates that the majority die before two years have elapsed following the inception of the symptoms of both diseases. In this special group of 43 patients only two succumbed within this period of time, while 13 have lived from five to ten years and 6 are living from eleven to fourteen years with both diseases present. Accordingly, one must realize that the coexistence of pulmonary tuberculosis and diabetes mellitus does not always prove rapidly fatal for the patient so afflicted. It is probable that such cases of fibroid tuberculosis in the diabetic are more frequent in private practice than among the patients admitted to Montefiore Hospital and that the general mortality is not as great as this study would indicate. A good example of this type-course is the following case:

Case 5: L. F., no. 149–18299, a man, aged forty-eight, was admitted to Montefiore Hospital in December, 1929, with a history of cough, slight fever and haemoptysis in 1925. Diabetes mellitus was discovered a few months before admission to the hospital, and the patient was placed on a restricted diet without insulin. Physical and roentgen examinations on admission revealed numerous fibrotic tubercles in both upper lobes and two large cavities in the right upper lobe. The sputum was positive for tubercle bacilli. The patient

was afebrile on admission and continued so throughout his stay in the hospital. Since discharge he has been under observation in the out-patient department and he has remained well to date. The tuberculosis has continued to be inactive for five years despite the presence of a cavitated pulmonary process associated with diabetes mellitus.

Included among the 43 cases discussed, there were 9 instances which followed a very benign course in which there was only minimal fibrotic pulmonary tuberculosis discovered by roentgen examination. Seven of these patients had had symptoms which attracted attention to their lungs, such as cough, haemoptysis or fever previous to their admission to the hospital. Repeated sputum examination failed to reveal the presence of tubercle bacilli in all of them. The course of their tuberculosis following admission to the hospital and following their discharge was asymptomatic. Repeated roentgen studies over a period of several years have failed to reveal any alteration in the pulmonary process. The other 2 cases of this group were discovered on the general diabetic service during routine chest examinations. Sputum examination was negative for tubercle bacilli, but the roentgenogram revealed scattered fibrotic tubercles. No symptoms referable to the chest were present at the time tuberculosis was diagnosed and none have developed subsequently.

In a recent paper Wessler and Hennell (12) describe a group of cases of pulmonary tuberculosis with diabetes in which evidence of resorption or resolution of the lesions occurred (so-called "benign pulmonary tuberculosis with diabetes"). While evidence of resorption, sometimes to a large degree, was noted on roentgen examination, and, while in several instances the outlines of cavities originally seen on the roentgenogram could not be detected later, the disease either continued to progress or became chronic. Complete resolution was not observed in this series. The following history illustrates this type of course:

Case 6: M. W., no. 22612, a woman, aged sixty-two, was admitted to Montefiore Hospital in September, 1932, with a history of having had diabetes, accidentally discovered in 1928. In January, 1931, she was admitted to another hospital because she had lost 30 lbs. in three months and coughed a little. Roentgen examination at that time was reported to show pneumonic tuberculous infiltration in the right upper lobe. During her stay in that hospital, the roentgen appearance of this consolidation became less opaque, her clinical course asymptomatic and she was discharged in February, 1931, as a case of benign tuberculosis in the diabetic. She felt fairly well until September,

1932, when because of recurrence of cough, loss of weight and weakness, she was admitted to Montefiore Hospital. Physical and roentgen examinations on admission revealed an extensive consolidation of the right upper lobe and some infiltration of the middle and lower lobes. During her stay in the hospital, in spite of the fact that the patient remained afebrile and gained weight, there was an extension of the pulmonary tuberculosis and cavitation appeared in the right lower lobe. In an attempt to control the spread of the disease, artificial pneumothorax was induced on the right side, with apparently excellent results. The patient's general condition continued to improve, the sputum became negative for tubercle bacilli, and she was discharged in August, 1933, to the out-patient department. In January, 1934, pneumothorax refills could no longer be continued because of an obliterative pleuritis. However, she continued to feel fairly well until April, 1934, when an exacerbation of pulmonary symptoms of cough, expectoration and weakness occurred. Roentgen examination at this time revealed not only the old tuberculosis in the right lung, but also a fresh exudative process and cavitation in the left upper lobe.

Though showing evidence of remissions this patient suffered a severe exacerbation. It may be that, with more prolonged observation, many of the diabetic patients in whom the tuberculosis has shown apparent absorption will suffer severe and fatal exacerbations.

In 13 cases the pulmonary tuberculosis definitely antedated the diabetes, and in these, the pulmonary tuberculosis had apparently existed from four to thirty-three years prior to the development of the diabetes. The tuberculosis history in these patients was always quite definite. Many of them had taken the "cure" at sanatoria, some at Bedford Hills, and in all of them the tuberculous process had become clinically arrested. Most of them had been without any symptoms referable to their pulmonary disease for many years prior to the present recrudescence. The diabetes mellitus manifested itself at the average age of 46.1 years. In this group likewise, the women developed the disease at a slightly younger age (average 44 years). The onset of the diabetes was simliar to that noted in the nontuberculous. Extreme loss of weight, polyuria, polydipsia, pruritus and weakness were the symptoms which helped establish the diagnosis. The type of diabetes encountered varied; 7 cases were mild and in 6 the diabetes was moderately severe. The reactivation of the quiescent tuberculous process apparently did not depend upon the type of diabetes, for, in each group the time it took for the tuberculosis to reëstablish itself as an active clinical process was practically the same. The average time-interval between the onset

of the diabetes and the reappearance of clinical tuberculosis was less than two years.

The course of the pulmonary disease presented some very striking features in this group. The average duration of life after both diseases were diagnosed was much longer than in the group in which diabetes appeared first. No deaths occurred under one year and only 4 patients succumbed during the one- to two-year period, by which time in the larger group the majority of the patients had died. There were 6 deaths in periods ranging around three to six years. The other 3 patients are alive and under treatment, one of them after thirteen years. The tempo of the progress of the reactivated tuberculous disease does not appear to be as rapid in those cases in which an arrested tuberculosis antedated the onset of diabetes mellitus. The following clinical abstracts illustrate the foregoing points:

Case 7: I. P., no. 151–18603, a woman, aged forty-eight, was admitted to Montefiore Hospital September 8, 1928, with a history of having had pulmonary haemorrhages in 1911, at the age of thirty-one. Following this, no other symptoms of active pulmonary disease occurred and she felt well until 1925, when mild diabetes mellitus was found to be present. This was easily controlled on a low carbohydrate diet without insulin. Later that same year, she began to suffer from loss of weight and weakness, which was soon followed by cough and expectoration. Examination on admission to the hospital revealed a well-nourished woman with mild diabetes, and a bilateral tuberculous infiltration throughout both lungs, with a large cavity in the right upper lobe. Sputum examination was positive for tubercle bacilli, and the temperature range was mildly febrile. Despite the steady progression of the tuberculosis during the patient's stay in the hospital, she maintained her weight and feeling of well-being until January, 1930. Afterward, the fever became hectic, she appeared toxaemic and died on June 25, 1930, almost five years after the presence of both diseases had been noted.

Case 8: A. K., no. 173–19953, a woman, aged sixty-one, was admitted to Montefiore Hospital July 20, 1931. In 1888, at the age of eighteen, she had haemoptysis and was ill for several months. She rested and felt well, with no symptoms referable to her chest. In 1921, following polyuria, diabetes mellitus was diagnosed. On simple dietetic measures she was well until November, 1930, when she became comatose. Afterward, she coughed, and in 1931 the sputum became blood-streaked. From November, 1930, to July, 1931, she lost 58 lbs. and became very weak. On admission to the hospital, she was still fairly well nourished, her diabetes mellitus was moderately severe,

and she had consolidation and cavitation throughout the right upper lobe and scattered tubercles in the rest of the lung. Her temperature reached 101°F., and the sputum was positive for tubercle bacilli. For the past three years she has been continuously febrile and bedridden. However, her condition has not changed materially. She has had both diseases for fourteen years with active tuberculosis for the past four.

These cases indicate that the clinical course of pulmonary tuberculosis in the diabetic is as a rule continuously active and progressive to exitus. Exceptions to this rule occurred in a small number of patients including some who had exacerbations and remissions, some with minimal fibroid lesions which never became active and some where the old tuberculous process had antedated for a long period of time the onset of diabetes and the recrudescence of the tuberculosis.

6. FATAL HAEMORRHAGE IN THE TUBERCULOUS DIABETIC

Fatal pulmonary haemorrhage in the tuberculous diabetics in this group occurred much more frequently than it did in the nondiabetic patients at Montefiore Hospital. On the general service it was estimated that 6.8 per cent of the deaths were the result of terminal haemorrhage. Of the 130 deaths which occurred in the hospital among the diabetic group, 17 patients died of a fatal haemorrhage, an incidence of 13 per cent. If we include only those over fifty years of age, 17.7 per cent died as a result of bleeding. Only two deaths from this cause occurred in patients under fifty years. This would seem to lend weight to the view that fatal haemorrhage was influenced by the sclerotic condition of the vessels found in the older age-group. Blood-pressure readings taken during the hospital stay, however, failed to reveal any specific relationship between a heightened pressure and the occurrence of haemorrhage. Sex appeared to play no part, as 9 patients were men and 8 were women. This finding of an increased incidence of fatal haemorrhage in the diabetic varies from the opinions of Joslin (7) and Van Noorden (13) and agrees with the views expressed by Fishberg (9).

In the majority of the cases, 13 of 17, the disease in the lungs was running an active progressive febrile course with, as a rule, extensive bronchopneumonic infiltration and cavitation at the time the terminating haemorrhage occurred. Four of the patients were getting along fairly well, and were ambulant and afebrile when haemoptysis started, ending in a fatal haemorrhage. As a rule, several repeated smaller bleedings

antedated the fatal one. In only one case was the initial haemorrhage fatal; in all others there had been some history of blood-spitting.

The type of diabetes apparently did not influence the number of fatal haemorrhages, as 9 occurred in moderately severe, and 8 in mild cases of diabetes.

Six of the patients came to necropsy. In each of them there was definite evidence of bleeding into a cavity, but in only one was a ruptured aneurysm of a branch of the pulmonary artery found.

7. EXTRAPULMONARY TUBERCULOUS COMPLICATIONS IN THE DIABETIC

The diabetic as well as the nondiabetic with chronic tuberculosis suffers from extrapulmonary foci of disease. Seventeen men and 14 women had definite signs of laryngeal tuberculosis, an incidence of 14.2 per cent. The laryngeal involvement varied in type and extent as it does in the nondiabetic: in some there was merely a reddening of the cords with slight thickening in the interarytenoid region, while in others marked ulceration and oedema involved not only the vocal cords and surrounding structures, but also the epiglottis. Here, as in the cases in the general-hospital service, the type and progression of the laryngeal process usually went hand in hand with that of the pulmonary disease. However, the presence of tuberculous laryngitis made the prognosis much more severe as can be seen by comparing the following figures. Of 218 cases, 130 patients, 59.6 per cent, died in the hospital; of the 31 patients who developed laryngeal involvement 23, or 74.1 per cent, died during hospitalization. The average span of life after the laryngeal disease was diagnosed showed such marked variation that general conclusions cannot be drawn. In several of the favorable cases which had only "coxcomb" elevations in the interarytenoid regions or healed ulcerations, the patients lived for many years with improvement in both laryngeal and pulmonary lesions. Feeding, which is such an important part in the metabolic management, was often made more difficult because of pain and inability to swallow food. Often, insulin dosage had to be diminished because of lessened food-intake. Sometimes, although rarely, the patient's urine became sugar-free because of an actual self-imposed starvation regimen for the avoidance of pain. Tuberculous laryngitis is a complication which makes the treatment more difficult and the prognosis more severe.

Intestinal tuberculosis existed among these patients apparently to a lesser degree than in the nondiabetic groups. In only 29 were there

sufficient data, either clinical or at necropsy, to make the diagnosis of intestinal involvement tenable. In only 18 of a total of 49 autopsies was involvement of the bowel found, a percentage of 36.7. This figure is much less than that found on the general service, where a review of the autopsy material demonstrated an incidence of intestinal tuberculosis of 65 per cent (Fishberg (9)). Likewise, the extent of involvement was as a rule minimal, only the caecum and immediately adjacent structures being involved. The intestinal involvement occurred in those patients in whom the pulmonary disease was active and progressive.

Miliary tuberculosis and tuberculous meningitis occurred as a terminal event in 10 of the cases. Accordingly, 8.6 per cent of the hospital deaths were directly attributable to this complication. There were no unusual features in the development of this complication; the patients were all seriously sick and in every instance the lung lesion was very extensive. Clinically, headache, drowsiness, stupor, or change of personality suggested the diagnosis, which was then substantiated by lumbar tap and spinal-fluid examination.

Genitourinary tuberculosis was rarely encountered as part of the clinical disease picture in this group of patients. This is likewise in accord with the view that involvement of the genitourinary system is, as a rule, a late complication of pulmonary tuberculosis, and that, because of the rapid progression of tuberculosis in the diabetic, such complications do not develop.

Spontaneous rupture of the lung with resulting pneumothorax occurred with somewhat increased frequency in these diabetics. There were 9 instances, or 4.1 per cent, of spontaneous pneumothorax among these 218 cases. Various authors have estimated the frequency of this complication among tuberculous patients as from 0.73 to 3.1 per cent. Spontaneous pneumothorax occurred in the patients at Montefiore Hospital in 3 per cent of all the cases upon the wards. This increased incidence among diabetics is probably the result of the rapid evolution of their pulmonary tuberculosis.

8. CARDIOVASCULAR COMPLICATIONS IN THE TUBERCULOUS DIABETIC

The impression that arteriosclerosis and the attendant complications such as gangrene, coronary-artery disease, and other manifestations of hypertension exist more frequently in the diabetic, has gained a wide belief among the investigators of diabetes mellitus. We have attempted

to analyze our group of cases with this special point in mind, and to see whether the presence of tuberculous disease may have altered the cardiovascular findings. It seemed advisable to separate this study according to age-groups (decades) in order to get a truer evaluation as compared with the usual findings in each age-group.

Out of the 24 cases in the thirty-one to forty age-group, there were only 3 instances of clinical or pathological evidence of cardiovascular disease:

Case 9: The first patient, a man, had had two amputations of the lower extremities for gangrene before the development of his tuberculosis and his admission to Montefiore Hospital. While in this hospital a further amputation of his left leg had to be performed for spreading gangrene. During all this time his blood-pressure registered 86/50. The tuberculous process was a chronic one, with cavity and positive sputum, but without signs of tuberculous toxaemia. Death occurred as a result of coronary-artery disease.

Case 10: A man with active progressive tuberculosis complicating mild diabetes of two years' duration. His blood-pressure was 128/72. Because he complained of severe pains, a roentgen study was made of his legs and revealed arteriosclerotic changes. There were no evidences of sclerotic changes elsewhere.

Case 11: A man who was on the wards first at age thirty-one. At that time he had diabetes and an active progressive tuberculosis for which pneumothorax was given successfully. On admission his blood-pressure registered 135/85. While on bed-rest and during his febrile course, the pressure dropped and remained 90/60. He continued under observation and now, at the age of forty-two, attends the out-patient department where his blood-pressure readings are uniformly 145/90, with no clinical symptoms referable to the pressure.

These case abstracts are rather fully presented because they illustrate well the types of change which may be considered secondary to cardiovascular pathology. Rarely does one find a case of extensive gangrene and with extreme rarity definite coronary closure. More frequent is the presence of painful extremities resulting from vascular changes, and asymptomatic increases in tension.

Of the 62 patients between forty-one and fifty, 12 gave evidence of some vascular change. Six presented signs of systolic hypertension only, with the readings varying from 170/80 to 145/90, with no symptoms referable to the increased tension. Four instances of gangrene

were found, in three of which the gangrene and amputation took place before the tuberculous disease in the lungs was established; in the other the gangrene apparently followed a hot-water-bottle burn. One patient presented signs of advanced "diabetic retinitis" and survived for ten years, but still has visual disturbances. In another instance, postmortem examination revealed sclerosis of the vessels of the extremities. Considering these 62 cases as a whole, they suffered very little from any cardiovascular symptoms occurring subsequent to the development of their tuberculosis.

Seventy-two cases were in the age-group of fifty-one to sixty. Thirty presented signs of some vascular change. Twenty-one had hypertension, but in this age-group there were, as a rule, definite symptoms accompanying the rise in pressure. Three men suffered from definite coronary occlusion. One man entered the hospital at the age of fifty-six with a tension of 115/65, suffering from mild diabetes and fibrotic tuberculosis with cavity. During a four-year stay in the hospital his pressure had risen to 210/110, and he developed a right hemiplegia which persisted. No marked change occurred in either his tuberculous or diabetic disease. One year subsequent to his hemiplegia, he died from what appeared to be mesenteric-artery occlusion. Two patients had intermittent claudication which gave rise to considerable pain and one had signs of congestive heart-failure. The other 15 presented no noteworthy symptoms in association with the hypertension. Among the 9 cases without hypertension, but with vascular changes, there were two cases of gangrene, in both of which the pressure was 120/70. In one instance a case was admitted to the wards with a left hemiplegia which had occurred three years before the onset of the symptoms of tuberculosis. The blood-pressure readings were low and the pulmonary process active, and death occurred two months after entry. In 3 other instances of this low-tension group, in which no special symptoms occurred suggestive of cardiac involvement and in which death appeared to be directly due to active tuberculosis, postmortem examination revealed varying degrees of coronary and generalized vascular sclerosis. One patient developed rapid congestive failure with bilateral hydrothorax, and at autopsy extensive coronary involvement with cardiac fibrosis was found. In two other instances, routine roentgen examinations revealed calcified plaques in the arch of the aorta, but no symptoms of cardiovascular disease were present.

In this age-group we had our largest number of cases, and 41 per cent

of them presented some evidence of vascular change either during life or at necropsy. The usual types of vascular injuries were encountered either with or without the presence of hypertension. In 7 cases, or 9.7 per cent, coronary closure was found; however, in only 4 cases did it play any part in the clinical picture. Gangrene of the extremities occurred only twice, and hemiplegia was present in the same number. In recapitulating these findings, it did not seem to us that, in this age-group of diabetics afflicted with tuberculosis, cardiovascular disease *per se* either gave rise to symptoms with any marked degree of frequency or added unduly to the percentage of deaths.

Forty-two patients were in the age-group sixty-one to seventy. Twenty-six presented some signs of vascular change. Fifteen had hypertension ranging between 220/130 and 140/94. There were quite a number with a definite increase in the diastolic pressure. In this hypertensive group, 7 cases were completely asymptomatic, while 3 others had only roentgen evidence of aortic calcification. One, with sclerotic tuberculosis, which was found only postmortem, had gangrene which required amputation of the right foot. The one with the highest tension revealed extensive arteriolar sclerosis postmortem. One patient suffered from hypertensive heart disease, anginoid pains and intermittent claudication with a tension of 190/100. One other, in whom the tuberculous process was extensive but inactive, had multiple cerebral vascular insults, with aphasia, loss of consciousness and right-sided weakness. Gangrene of the extremities was present in another case with a tension 146/76, and postmortem there was found coronary occlusion which had given no clinical evidence of its presence. This association of gangrene and coronary-artery disease, which has been emphasized by students of cardiovascular disease in diabetes, was not found frequently in these cases. In one other case of gangrene, which began two years before the onset of the tuberculosis, a right hemiplegia developed.

In the low-tension group, 5 cases of coronary thrombosis or sclerosis were found postmortem in which the tension during life on our wards never registered as high as 140 systolic.

This analysis of the 218 cases of diabetes mellitus and pulmonary tuberculosis, in so far as their cardiovascular status is concerned, revealed the following general figures: Forty-six cases registered the blood-pressure readings of hypertension. This represents 21 per cent of cases with hypertension at an average age of fifty-three years. The average

figure reported by the majority of authors is 34 per cent of hypertension in the nontuberculous diabetic at fifty years and those reported by Enklewitz (14) among the nontuberculous diabetics in the same age-group at Montefiore Hospital was 44 per cent. It would appear therefore that the presence of pulmonary tuberculosis lowered the incidence of hypertension in the diabetic. These cases likewise demonstrated that the blood-pressure even when raised was rarely above 160 systolic, and that diastolic tension above 100 was rare. Of the hypertensive cases, 15 patients had definite lesions associated with the increased tension, and 31 presented no symptoms or signs relative to the cardiovascular system. One hundred and seventy-two patients had either a normal or low blood-pressure, of which number 36 presented cardiovascular lesions either during life or at necropsy. The total number therefore of both the high- and low-tension groups which presented definite clinical or pathological changes was 51, or 23.3 per cent.

Gangrene of the extremities was encountered in 11 patients (5 per cent), of which 9 were men and 2 women. In a similar but nontuberculous age-group, reported by Enklewitz (14), 20.6 per cent developed gangrene of the extremities. In four, gangrene occurred many years before the onset of tuberculosis. In 2 cases it developed three years before the tuberculosis. In 5 cases the gangrene developed during the clinical course of the tuberculous disease. Four of these patients had coronary sclerosis or thrombosis. Intermittent claudication was complained of in four other instances, all in men. These complications of gangrene or intermittent claudication occurred only once before the age of forty, and in that individual an additional diagnosis of syphilis had been made.

Coronary-artery sclerosis, with or without thrombosis, was found twelve times. Eight developed a definite coronary syndrome. Of these six died with evidence of coronary thrombosis, and in four sclerosis of the coronary vessels was observed at autopsy. Two are still living, though suffering with dyspnoea and precordial pain. Eleven of the total number occurred in men and only one in a woman, discovered incidentally at necropsy. The disease was found in only one patient below the age of fifty years.

There were 2 cases of hypertensive heart disease, both of which had anginoid symptoms. These patients were suspected of having coronary-artery disease. Both died of advancing tuberculosis and the coronaries were found to be normal postmortem.

Cerebral vascular accident, resulting in hemiplegia or cerebral thrombosis, occurred in 4 patients. In two the paralysis started many years before the development of tuberculosis, and in two paralysis became manifest while the patients were in the hospital.

9. DIABETIC STATUS

In the 218 cases diabetes of varying severity was enountered. There appeared to be no relationship between the severity of the diabetic process and the type of tuberculous disease encountered in the lungs. Among the mildest cases of diabetes one would often find widespread pulmonary tuberculosis running an active course, causing the death of the patient very rapidly; in some of the severest cases of diabetes the tuberculous disease assumed a milder slowly progressive course.

Clinical Aspects of the Diabetes: The study of ketosis among these patients revealed some facts of interest. It was a rare occurrence on the wards during the period of hospitalization while the patient was under adequate dietary and insulin control. However, as a terminal phenomenon, it was observed in 8 patients, usually in association with an acute clinical episode which suddenly changed the course of the patient's illness. Thus ketosis occurred terminally in 2 patients with tuberculous meningitis, one with a rapidly spreading gangrene of the extremities, one with a necrotizing pneumonia, one with an acute gastric dilatation, and two with marked gastrointestinal symptoms due to the appearance of intestinal tuberculosis. However, as the first or one of the prime indications that tuberculosis had invaded the lungs of the diabetic, ketosis was not infrequent. Of 5 patients who had been treated on the diabetic wards of the hospital and had no tuberculosis, three acquired it with the occurrence of diabetic acidosis at the onset. Four other patients had a history of diabetic coma with the onset of their pulmonary tuberculosis and, while being hospitalized for the coma, pulmonary disease, which appeared to be of recent acquisition, was discovered. The oldest of these 7 patients was twenty-nine years of age. Of the patients under twenty years of age, 80 per cent had coma or ketosis as an indication of the onset of the pulmonary process.

Ketonuria was found to be present in 35 patients at the time of their admission to the hospital. In them, the tuberculosis was usually of fairly recent origin as the following figures indicate: Eight had their pulmonary symptoms less than three months, 12 less than six months, 5

less than one year, and 2 slightly more than one year before admission to our wards. Seven had inactive pulmonary tuberculosis which had become reactivated less than six months prior to hospitalization. These cases of ketonuria were found in all age groups, but much more frequently under the age of forty. It would appear that the advent of pulmonary tuberculosis in the diabetic is frequently followed by a definite change in the patient's metabolism, as manifested by the appearance of diabetic ketosis and coma at this time. Additional facts which tend to support this view were obtained from the histories of 21 patients who left the hospital and were later readmitted. In 5 instances there had been no reactivation of the tuberculosis and the patients had been readmitted because of haemoptysis, spontaneous pneumothorax or hemiplegia, and in none of them was there any evidence of a change in the diabetic status. Sixteen were readmitted with a spread or reactivation of the pulmonary disease, and five of them were suffering from diabetic ketosis, while 6 others were found to need larger doses of insulin than they had required during the quiescent phase of the pulmonary disease.

In accord with the views expressed by most authors, as death approached, the diabetic management often ceased to be a problem. Self-imposed starvation, as a result of complete lack of appetite, would cause glucose to disappear from the urine, and it is probably because of this terminal phenomenon that the belief arose that active pulmonary tuberculosis makes diabetes mellitus less severe.

Dietary Treatment of the Tuberculous Diabetic: The decade in which this group of patients was admitted to Montefiore Hospital was one in which the dietary treatment of diabetes was modified by the introduction and use of insulin therapy. Naturally, during this period both the type of diet and the manner of administration was in a state of flux at Montefiore Hospital as well as elsewhere. Prior to 1923 tuberculous diabetics were treated on the principle of undernutrition introduced by Allen and applied to the tuberculous diabetic by Landis, Funk and Montgomery (1) in 1919, and by Janney and Newell (15) in 1920. In 1923, four patients of the group were treated with a diet low in carbohydrates and containing less than 1,600 calories per day. The large loss in weight which is characteristic of these two diseases continued, and emaciation and death followed rapidly.

Dietary management on the wards has varied considerably during the decade covered by this investigation. In the years, 1923–1926,

the patient on admission was placed on a weighed diet of approximately 50 gm. carbohydrate, 75 gm. protein, and 175 gm. fat. Each patient was given a separate weighed diet, which was varied in its individual constituents, in an attempt to achieve diabetic equilibrium. If the basic diet resulted in no glycosuria, the carbohydrates were cautiously increased, and, if normal urinary and blood findings were not restored, small doses of insulin were used. This method of feeding patients with weighed individual diets proved uneconomical, but, as part of the pre-insulin tradition, it was slow in disappearing. The high fat diet that was necessarily employed was not relished or enjoyed by the patients. Soon it was realized that a greater proportion of carbohydrates was preferred and that this could be given without increasing the difficulty in controlling the diabetic status of the patient. Accordingly, a basic diet of 75 gm. carbohydrate, 75 gm. protein and 150 gm. fat was instituted, but each diet was weighed and varied in an attempt to control the glycosuria. During this period of use of the individual weighed diet, many weeks would often elapse before the patient established diabetic equilibrium, and during this time continued loss of weight and strength militated against the general feeling of well-being.

At present, a basic diet has been established for all diabetics on the tuberculosis service of 150 gm. carbohydrate, 75 gm. protein and 100 gm. fat. Since the abandonment of the undernutrition diets, the patients have been fed between 2,100 and 2,300 calories a day, and those patients, who were not extremely ill or toxic, were able to gain from 2 to 4 lbs. weekly. In view of this experience, it is difficult to understand the use of diets containing more than 2,400 calories in the treatment of the tuberculous diabetic. No diet employed resulted in any change in the character of the tuberculous lesion in the lung. Some authors have presented data in which high carbohydrate diet and large doses of insulin brought about rapid gains in weight, but investigation reveals that these were in patients in whom the tuberculosis was essentially productive and fibrotic. Similar patients with inactive tuberculosis on the wards at Montefiore Hospital gained just as rapidly with less heroic measures.

Glycosuria is controlled by the use of insulin, and diabetic equilibrium is usually reached within four to six days. Another advantage of this diet is that it is easily followed by those patients who become well enough to leave the hospital. After leaving the hospital they are able to carry on their daily routine without loss of weight.

Appetite plays an important rôle in the feeding of the patients and, aside from periods of sudden reactivation of the pulmonary disease and in those patients who are moribund, the appetite of the tuberculous diabetic remains good. As a result of this, even patients who run a febrile course gain weight. However, loss of appetite may be a cardinal symptom of a fresh tuberculous involvement in a case that appears to be progressing favorably on the ward or in the dispensary and in which the tuberculous disease again becomes active.

Ketosis appearing in any of the patients at Montefiore Hospital is treated as a medical emergency. An enema is first given and, if there is nausea or vomiting, gastric lavage is done. Large quantities of fluids are given by mouth if possible, or by the intramuscular or intravenous route. Glucose and insulin are given in amounts varying with the severity of the ketosis, as determined by hourly urine examinations. Even in those patients who have entered the hospital in a well-established coma, there has been little difficulty in controlling the acidosis with this routine.

In the presence of symptoms of gastrointestinal tuberculosis, an attempt is made to provide a soft nonresidue diet containing proportions of food values similar to the general diabetic diet. Such large quantities of food seem to be well tolerated. The plan of nutrition which has been evolved for the tuberculous diabetics has developed along the following lines: The first step was the abandonment of the undernutrition principle because it could not be successfully used in the presence of two wasting diseases. The use of the individual weighed diet proved to be uneconomical and impractical, and, when variations in diet were depended upon to establish diabetic equilibrium, the required period often lasted from four to five weeks, and during this period the patient lost weight and strength. To-day each patient with a combination of tuberculosis and diabetes receives a diet similar to that of all other tuberculous diabetics, with a rather high carbohydrate proportion. Sole reliance in obtaining control of the diabetes is placed upon the liberal use of insulin with the diet containing sufficient food to provide for rapid gains in weight if the food is completely utilized. This dietary regimen has shortened the period required to obtain diabetic equilibrium from weeks to a few days, and has permitted the handling of large groups of such patients more economically.

Insulin in the Treatment of the Tuberculous Diabetic: Insulin was used solely with the object of improving the nutrition of the patient. The

dosage was governed by the patient's ability to utilize the standard diet of 150 gm. carbohydrate, 75 gm. protein and 100 gm. fat, to which were added one or two glasses of milk and one or two slices of bread between meals. Eighty-eight patients received no insulin, either because their diabetes was very mild or, if severe, they could not consume their food because of the active febrile tuberculous process. One hundred and seven patients were given from 10 to 40 units of insulin daily, which succeeded in controlling the glycosuria and was easily given in two equal or slightly dissimilar doses. Twenty-two patients required from 50 to 90 units of insulin daily which was split into three doses with the morning dose larger than the mid-day dose, which in turn was smaller than the evening dose. Patients requiring this amount of insulin usually had a high fasting blood-sugar.

In view of the suggestion put forward by Lundberg (16), Wassmund (3), and others, that the use of insulin may be followed by the reactivation of a dormant tuberculous process into an active exudative and progressive one, this group was analyzed from this viewpoint. This study was to include the determination of the frequency of haemoptysis and fatal haemorrhage because it also has been stated that the use of insulin among tuberculous patients increases the incidence of these complications. We shall not enter into a discussion of the theoretical possibilities concerned with the nonspecific protein reactions, but limit our investigation to an analysis of our own observations. However, if insulin therapy is to be called upon to share the responsibility of reactivating pulmonary tuberculosis, it seems reasonable to demand that the onset of the tuberculous process should date soon after the inception of insulin therapy. Of the 218 patients in this series, only 37, or 16.5 per cent, had used insulin prior to the beginning of their pulmonary tuberculosis, and, of this number, 21 used insulin from three to eight years before the tuberculosis became active. The remainder of this special group developed their active pulmonary disease within two months to two years after insulin therapy had been instituted. It is obvious therefore that clinically no causal relationship can be established between the administration of insulin and the development of pulmonary tuberculosis. As an additional argument in support of this view, we may cite the following facts: In this group there were 13 patients who had suffered from pulmonary tuberculosis early in life, who had received proper treatment, in whom the tuberculosis became inactive, and who had felt well for many years. Later, when they reached middle age, diabetes mellitus appeared. Although the tuberculosis became active

again in all 13 cases, only two received insulin therapy prior to the reactivation, and in these 2 instances reactivation occurred four months and three years, respectively, after the institution of insulin therapy. These facts would tend to support the belief that the administration of insulin plays no large rôle in the reactivation of pulmonary tuberculosis in the diabetic.

Sixty-four patients received their first insulin therapy after hospitalization at Montefiore, and in these it was possible to observe the effects of this therapy. Of these, 35 died in the hospital, and the clinical course and repeated roentgen studies did not reveal any change of the pulmonary disease from exudative to sclerotic tuberculosis or *vice versa*, which could be ascribed to insulin therapy. There was, however, marked symptomatic improvement in many who received insulin for the first time. This improvement consisted of a subjective sense of well-being together with a gain in weight and strength, often in spite of the presence of fever. The pulmonary symptoms and the fever were not influenced in the slightest degree by the use of insulin.

In 6 patients who had extensive fibroid pulmonary tuberculosis, insulin therapy did not convert the quiescent lesion into an active one. In 5 other instances the patients were suffering from active febrile pulmonary tuberculosis. Insulin did not change the course or character of the disease, but the tuberculosis became quiescent after the induction of therapeutic pneumothorax.

Among the 64 patients in whom insulin was used for the first time at Montefiore Hospital, 29 gave a history of haemoptysis prior to hospitalization and the use of insulin. Only four of these continued to have blood in their expectoration following the use of insulin. Thirty-two patients had no haemoptysis prior to admission to the hospital and, of these, only 3 developed bloody expectoration. It is no more likely that insulin caused these haemoptyses than that it prevented a recurrence in those who had previously spat blood. Of the 130 patients who died, 89 received insulin therapy for some time before their death, and of this number 13, or 14.6 per cent, died with terminal haemorrhage. In the 41 instances in which insulin therapy had never been employed, 5 patients, or 12.2 per cent, died with terminal haemorrhage. Accordingly, the belief that insulin therapy increases the frequency of haemoptysis and fatal haemorrhage in the tuberculous diabetic is not supported by these facts.

Although both local and systemic reactions to the use of solutions of

insulin have occurred in the patients, these reactions have never been followed by the appearance of fever or clinical or roentgen evidence of increased activity of the pulmonary tuberculosis. This point is illustrated by the following case:

Case 12: J. L., no. 11649, a woman, aged twenty-eight, had been admitted five times in the past six years with exacerbations of her pulmonary tuberculosis. In one instance the exacerbation followed directly upon an overdose of tuberculin used as a diagnostic test. The reaction was typical, with high fever in thirty-six hours, and a widespread exudative process in the lungs, all of which rapidly subsided. During later stays in the hospital, the patient developed both local areas of erythema and generalized urticaria which appeared to be directly due to the administration of insulin, without any evidence of fresh tuberculous activity either clinically or radiologically.

No pulmonary reactivation was ever found in any of the cases following local or general reactions to insulin.

An analysis of the 64 cases in which insulin therapy was first instituted at Montefiore Hospital, does not reveal any evidence that insulin can convert an exudative lesion in the tuberculous diabetic into a relatively benign one. It neither decreases nor increases pulmonary symptoms. Pulmonary tuberculosis in the presence of diabetes not infrequently remains sclerotic and quiescent throughout life with or without insulin therapy, and, when the pulmonary disease is active, it will continue so with or without insulin therapy. Collapse therapy in properly selected cases is the only known means of artificially converting an active pulmonary tuberculosis into a quiescent one, and this statement holds true for the tuberculous diabetic.

The complications encountered from the use of insulin have been touched upon, but they will be somewhat elaborated in the following paragraph. Local erythema at the site of injection and at times generalized urticaria resulted. These allergic reactions disappeared rapidly with change of the brand of insulin used and, after a short rest, the offending brand could be used again without causing a similar reaction. Hypoglycaemic reactions are not infrequent in the tuberculous patient receiving insulin and must be constantly guarded against. Frequently, patients have complained of a more or less severe feeling of dizziness, faintness and weakness, with a tendency toward a cold, clammy perspiration following insulin injections. To overcome this, the following routine has been established at Montefiore Hospital: No single dose of

insulin larger than 40 units is ever administered. Insulin is given subsequent to meals and the dosage is governed by the amount of food which the attendant observes has been eaten at a given meal. Accordingly, there may be a large variation in the dosage, depending upon the patient's appetite and ability to ingest his diet. It is likewise the custom to allow a glycosuria up to 10 gm. daily, which protects the patient against a serious hypoglycaemic accident and at the same time permits the use of a rich enough diet to enable the patient to gain in weight and strength.

10. THERAPEUTIC MANAGEMENT OF THE TUBERCULOSIS

The treatment outlined for the tuberculous disease encountered in these patients was along the well-accepted principles which have been universally adopted in all tuberculosis institutions. The cases were first classified by the resident and attending staffs, after complete history, physical and roentgen examinations had been performed, into those running a dynamic and an adynamic course. The fibroid inactive cases were merely given custodial care. The active febrile and exudative processes were treated primarily with bed-rest and active nursing and medical supervision. Supporting treatment and the administration of various medicaments were resorted to, whenever symptomatic relief was indicated. An attempt was made to place the patients into a separate ward-unit, to ensure a closer watch on their progress and an easier supervision of the diet and insulin given.

However, in spite of the splendid general care with which these patients were handled, the overwhelming majority died of a steady progression of the tuberculous disease or its attendant complications, such as fatal haemorrhage, miliary tuberculosis, or spontaneous rupture of the lung.

Collapse therapy was the only therapeutic measure capable of altering a rapidly developing, active exudative tuberculosis into a quiescent process. In properly selected cases, the results attained were very striking. A toxic tuberculous bronchopneumonia, with an almost positive rapidly fatal prognosis, was not infrequently controlled by pneumothorax, so that the pulmonary process became either actually arrested or at least quiescent. Cases were selected for pneumothorax therapy only on the basis of an active progressive process in the lungs, when none of the accepted contraindications such as bilateral extensive disease, advanced laryngeal or intestinal tuberculosis were present. If the pa-

tients did not respond favorably under a strict bed-rest regimen, pneumothorax therapy was suggested, irrespective of the type of diabetes or the age of the individual.

The results attained by induced pneumothorax were comparable to the results reported in the nondiabetic, in spite of the fact that we did not consider age as a contraindication to collapse (Wiener and Kavee (17)).

11. PROGNOSIS

Analysis of Fatal Cases: Causes of Death: Of the 218 patients, 159, or 72.9 per cent, died, 130 in the hospital and 29 subsequent to leaving it. Among 124 men, 92, or 74.2 per cent, and among 94 women with both diseases, 67, or 71.2 per cent, died.

TABLE 3

Age and sex relationship of deaths to admissions

AGE	MALE			FEMALE			MALE AND FEMALE		
	Number admitted	Number died*	Per cent died	Number admitted	Number died*	Per cent died	Number admitted	Number died*	Per cent died
14–20	3	0	0.0	2	0	0.0	5	0	0.0
21–30	9	6	66.6	2	1	50.0	11	7	63.7
31–40	17	8	47.0	8	4	50.0	25	12	48.0
41–50	34	25	73.5	28	11	38.6	62	36	58.1
51–60	37	25	67.6	34	21	61.7	71	46	66.3
61–70	24	14	58.2	17	13	80.4	41	27	65.8
71–over	0	0	0.0	3	2	66.6	3	2	66.6
Total.....	124	78	62.0	94	52	55.3	218	130	59.6

* Hospital deaths.

Analysis of the 130 cases of hospital fatalities as to age and sex (see table 3) reveals that *in all age-groups, the percentage of deaths was quite similar.* However, in accord with the greater number of admissions, the largest *number* of deaths occurred in the fifth decade. The duration of life following the onset of disease in these patients who died in the hospital was the same as regards all ages. Whether it was the second or fourth decade, the same proportion died in the six-month or longer period after both diseases became manifest. Apparently death was not contributed to by the cardiovascular changes of age.

Study of table 4, representing the duration of life after both diseases were present, as judged by pathognomonic symptoms, reveals the following: Of the 130 hospital fatalities, 38.4 per cent of the male deaths

and 30.8 per cent of the female deaths occurred within a period of one year following the detection of the presence of both diseases. The women in this one-year group apparently survived in larger numbers than the men. This percentage difference is continued in the two-year period, where we find that 69.2 per cent of the male deaths have occurred and 61.6 per cent of the female deaths. In the third-year period, a larger number of women died, so that by the end of the third year the percentages for the sexes was about equal, with about 75 per cent of the fatalities in the hospital occurring by the end of the three-year period. Of those patients who died in the hospital, only 12 men and 7 women having both diseases lived longer than three years.

TABLE 4

*Duration of life with both diseases**

DEATHS IN	MALE			FEMALE		
	Number	Per cent deaths	Cumulative per cent	Number	Per cent deaths	Cumulative per cent
years						
1	30	38.4	38.4	16	30.8	30.8
1–2	24	30.8	69.2	16	30.8	61.6
2–3	7	8.9	78.1	9	17.3	78.9
3–4	3	3.9	83.0	2	3.8	82.7
4–5	1	1.2	84.2	4	7.7	90.4
5–10	6	7.7	91.9	0	0.0	90.4
10–15	2	2.6	94.5	1	1.9	92.3
Not known	5	5.5	100.0	4	7.7	100.0
Total.....	78			52		

* Hospital deaths.

The cause of death in almost all cases was extensive bilateral, cavitating, active progressive pulmonary tuberculosis. Specifically, of the 78 men, 73 died of this cause and, of the 52 women, 48 fell into this group. Of the 5 men, whose deaths could not be attributed to tuberculosis, the cause of death was undetermined in one instance; one died from hypoglycaemic shock in the earlier years of the use of insulin (1924); one following the shock of an amputation operation; one of congestive heart-failure; and one of a vascular crisis, probably an infarction. Of the 4 women, one died of diabetic coma, 2 suffered from congestive heart-failure and in one the cause of death was unknown. Of these 7 cases, concerning which the clinical details are known, two also had severe and extensive pulmonary tuberculosis.

It seems proper at this time to emphasize again that the problem in the care of these patients is almost exclusively one of advancing tuberculosis. Dietetic regimens, variations in insulin dosages and all other measures, which have recently become popular, cannot be expected to alter very much the progress of the pulmonary process. Again we reiterate, these patients die of their tuberculosis and, while diet and insulin may and often do add to their weight and strength temporarily, the tuberculous disease eventually causes death.

Associated with the extensive pulmonary processes, 17 patients had fatal haemoptysis,—9 men and 8 women. Four men and 6 women had terminal meningitis. Spontaneous pneumothorax occurred as a contributory cause of death in 5 men and 3 women. In only 10 men and 4 women was a tuberculous laryngitis diagnosed. In comparison to the nondiabetics the percentage of laryngeal involvement was very small. Perhaps this is explained by associating the development of laryngeal complications with the duration of the illness, and in the diabetics the disease does not last long enough for the larynx to become involved.

Further analysis of the 130 cases of hospital fatalities reveals the fact that, practically without exception, there was no real remission in the tuberculous process. Neither by symptoms of activity nor roentgen studies were there to be found periods of definite improvement. In some the disease ran a fulminating course, the patients dying within a few months, while in others it pursued a more chronic course, permitting them to live longer. Those patients, few in number, who either left the hospital of their own accord or were discharged to continue the cure at home, were promptly readmitted because of marked accentuation of the symptoms of active tuberculosis. In many of them, the tuberculous process was progressing, with increased areas of caseation and cavitation, in spite of a rather marked gain in weight under diet and insulin. A detailed study of those cases of tuberculosis and diabetes, which terminated fatally in the hospital, leaves the impression that the pulmonary process is always advancing with no true periods of remission.

Follow-up of Discharged Patients: Of the 218 patients, 88 left the hospital alive. Eight of these patients have again been hospitalized, seven because of active pulmonary tuberculosis.

Twenty-six of them have disappeared. Efforts to trace them, either through the Department of Health, the social service department, or by personal investigation have proved unsuccessful.

Twenty-nine of the patients who left Montefiore Hospital alive have

died. In all but one, who died of congestive heart-failure, death was apparently due to extensive pulmonary tuberculosis. Twenty-four of these patients had extensive bilateral tuberculosis and were febrile when they left the institution. The duration of life of these patients after both diseases were diagnosed does not differ from that of the hospital deaths previously analyzed. Only 2 of the 29 patients lived more than fourteen months after discharge.

Thirty-three, or 15.1 per cent, of the patients are alive and traceable. Five of these had a combination of mild diabetes mellitus and minimal fibrotic tuberculosis. Their sputum was negative for tubercle bacilli, and there never were any clinical manifestations of tuberculous activity. There were also 3 patients with scattered fibrotic tubercles and one with fibroid phthisis, all with mild diabetes. None of these patients in the hospital or following discharge has been incapacitated in the slightest by the diabetes or pulmonary tuberculosis. They do not differ in this respect from similar individuals who are not diabetic.

The other 24 patients who left the hospital alive had active pulmonary tuberculosis while hospitalized. They were febrile and had positive sputum, and there was roentgen evidence of unilateral or bilateral cavitation. Only twelve of these are clinically well now. Ten patients are seriously ill because of their tuberculosis. Two patients have had several recurrent recrudescences of their pulmonary disease, which at the present time is regressing spontaneously. In only 5 instances has the disease been nonprogressive clinically, but the cavities have not disappeared nor is the sputum negative for tubercle bacilli. The patients' general condition is such that it may be termed quiescent but not arrested. Seven patients, all of whom received pneumothorax, are well and active, and doing their daily work. These patients have had neither pulmonary nor extrapulmonary metastases. Their cavities are closed and their sputum negative. There can be no better proof of the inefficacy of a policy of watchful waiting in the presence of diabetes mellitus and active pulmonary tuberculosis than this follow-up offers. One can only reiterate that collapse therapy must be resorted to early in the presence of progressive pulmonary tuberculosis and diabetes mellitus, and in properly selected cases great benefit can result from such collapse therapy.

12. ANALYSIS OF NECROPSIED CASES

Comparative Analysis of the Pathology of Tuberculosis in the Diabetic and Nondiabetic: Dr. David Perla (18), pathologist at Montefiore Hos-

pital, made an interesting comparative analysis of the 48 tuberculous diabetics which he had an opportunity to study. He selected another 48 cases similar in respect to age and sex, but without diabetes. While the total number is very small, still some very suggestive findings were encountered, having a particular bearing on the subject of whether or not any specific change could be ascribed to the presence of the diabetes (table 5).

In each group of the diabetics and nondiabetics, there were 33 men and 15 women of the same age-incidence, namely, forty between the ages of forty and seventy, and eight under forty years.

These similar groups were then studied for the following points: pleural adhesions, tuberculous bronchopneumonia, presence of extra-

TABLE 5

Comparative analysis of pathological changes in 48 diabetic and 48 nondiabetic patients with tuberculosis

	NUMBER OF CASES	SEX		AGE		PLEURAL ADHESIONS			TUBERCULOUS BRONCHO-PNEUMONIA		EXTRAPULMONARY TUBERCULOSIS				AMYLOIDOSIS	FIBROSIS	FIBROSIS WITH BRONCHIECTASIS IN UPPER LOBE	FATAL HAEMOPTYSIS
		Male	Female	40 to 70	Under 40	Both lungs dense	One lung dense	One lung free though tuberculous	40 to 70	Under 40	Larynx	Intestines	Miliary	Genitourinary				
Diabetics.....	48	33	15	40	8	14	22	9	18*	3	7	15	3	2	8	11	2	8
Nondiabetics.....	48	33	15	40	8	35	10	1	15*	4	9	19	3	4	14	24	17	3
Per cent diabetics.		70	30	82	18	30	45	18	86	14	14	31	7	4	18	23	4	18
Per cent nondiabetics.....		70	30	82	18	73	21	2	80	20	18	40	7	8	30	50	35	7

* Diabetic peak in fifth decade. Nondiabetic peak in sixth decade.

pulmonary tuberculosis, amyloid disease, fibrosis and bronchiectasis, fatal haemoptysis and necrotizing bronchopneumonia.

Dense pleural adhesions of both lungs were encountered in 14, or 30 per cent, of the diabetics, and in 35, or 73 per cent, of the nondiabetics. Dense adhesions over one lung and weak over the other were encountered in 22 of the former and in 10 of the latter. One lung free from adhesions, although involved with a tuberculous process, was found in 9, or 18 per cent, of the diabetics, and in only one, or 2 per cent, of the nondiabetics. This fact gives a ready explanation as to why it has been easier to establish a good therapeutic pneumothorax in the diabetics in an age-group in which pneumothorax has ordinarily not been induced or considered. A free pleural space, which the diabetics offer to a

much greater degree, is the main reason for our successful inductions at almost any age, a fact which is borne out by our clinical experience.

The variations found in the pleural adhesions of the two groups also fit in well with the concept that there is a more rapid development of the tuberculous process in the diabetic. Because of the accelerated tempo the process reaches a great extent of parenchymatous involvement before the pleura is implicated. The reverse happens in the slowly developing process in the nondiabetic. As a matter of fact, the one outstanding feature which appears to differentiate pulmonary tuberculosis in the diabetic from that in the nondiabetic is the greater rapidity of the evolution of the pathological changes. If we accept this concept as a working plan, we can then explain all the differential points still to be enumerated on this basis.

Tuberculous bronchopneumonia (table 5) occurred either as a terminal event or as a part of the rapidly fatal disease in approximately the same percentage of cases in each group. However, further analysis revealed the fact that the rapidly fatal complication occurred with much greater frequency a decade earlier in the diabetic group. This again emphasizes the more rapid development of the exudative parenchymatous process in the diabetic.

Extrapulmonary tuberculosis likewise presented some distinguishing features. Laryngeal involvement occurred in 7, or 14 per cent, of the diabetics and in 9, or 18 per cent, of the nondiabetics. Intestinal tuberculosis was found in 15, or 31 per cent, of the diabetics and 19, or 40 per cent, of the nondiabetics. While the differences are slight, they appear to be definite, and this fact also tends to strengthen the view previously emphasized. The same comment is true as concerns genitourinary involvement. Three cases of miliary distribution were found in each group, demonstrating no difference in the tendency toward actual gross haematogenous spread.

Amyloid disease was found eight times, or in 18 per cent, in the diabetic and fourteen times, or in 30 per cent, in the nondiabetic group. This again emphasizes the rapid course of the tuberculosis, for it is in our chronic cases that we encounter the larger percentage of amyloidosis.

Fibrosis and bronchiectasis were also found to differ quite widely in the two groups. Fibrosis of sufficient extent to deserve comment was found in only 11, or 23 per cent, of the diabetics, and in 24, or 50 per cent, of the nondiabetic cases. When one realizes that a large number of the patients were in the older age-groups, this fact stands out as quite

remarkable and to a degree unexpected. Along with fibrosis, but even more striking, is the difference in the absence or presence of definite bronchiectatic changes. In sluggish and chronic pulmonary tuberculosis, bronchiectasis occurs as a usual part of the pathological picture, especially involving the upper lobes. In these diabetics it was demonstrated in only 2, or 4 per cent, while in the nondiabetics it was found in 17, or 35 per cent. This again provides evidence supporting the concept that the tempo of the evolution of pulmonary tuberculosis in the diabetic is much more rapid than in the nondiabetic.

13. SUMMARY

1. Two hundred and eighteen cases in which tuberculosis and diabetes mellitus coexisted were studied at Montefiore Hospital during the decade ending December 31, 1932.

2. The age-incidence of those having both diseases differed in no wise from the expected age-incidence among diabetics in whom tuberculosis was not a factor: the average age was 54.3 years. The two diseases coexisted more than one and a half times as frequently among the women than among the men.

3. In accord with the view expressed by all authors, this series likewise demonstrates that the diabetes mellitus in the vast majority antedated the onset of the pulmonary tuberculosis.

4. Glycosuria and diabetes mellitus occurred rarely as a complication of active pulmonary tuberculosis; namely, in only 9 of the cases. However, a past history of tuberculosis, which may have remained arrested for years, does not render a patient immune to diabetes.

5. The onset of the tuberculous complication in the diabetic was often masked and insidious, and the definite diagnosis of the pulmonary disease rested upon the alertness of the examining physician in appreciating that the presence of a pulmonary infection is frequently the cause for difficulty encountered in controlling diabetes mellitus.

6. Final diagnosis often was made only from the roentgen film, since the type of process found in these cases often failed to give clinical signs of its presence.

7. Differing from the usual course of tuberculosis in the age-group involved, the disease, when manifesting itself in the diabetic, as a rule progressed steadily to death.

8. Of the 218 patients, 20.8 per cent died in less than one year, the disease running an acute toxic febrile course. In 47.2 per cent death

occurred within two years, and even though the disease appeared to be less toxic and the patient might even gain considerable weight, the process continued to progress uninterruptedly.

9. In only 43, or 17 per cent, of the 218 cases did the pulmonary lesion apparently seem to be arrested, at the time of discharge from the hospital. The nature of the diabetic process appears to play no part in determining the fate of the tuberculous process.

10. Of the 130 deaths, which occurred in the hospital, 17, or 13 per cent, were the result of a terminal haemorrhage, while it has been estimated that on the general service 6.8 per cent of the deaths were the result of this complication. This would indicate that there is an increased incidence of fatal haemorrhage in the tuberculous diabetic.

11. Laryngeal, intestinal and genitourinary tuberculosis existed much more infrequently in tuberculous diabetics, while spontaneous rupture of the lung with its resulting pneumothorax occurred with a somewhat increased frequency; namely, in 9 instances, or 4.1 per cent, of these 218 cases.

12. The analysis of the cardiovascular status revealed the following: 46, or 21 per cent, had hypertension at an average age of fifty-three years, which is a lower percentage of hypertension than is reported in the nontuberculous diabetic (44 per cent, Enklewitz (14)). The presence of active pulmonary tuberculosis decreases the incidence of hypertension in the diabetic. Eleven cases of gangrene of the extremities were found, but only 5 of these had developed during the clinical course of active tuberculous disease, the others having occurred before the onset of the pulmonary process. Coronary sclerosis, with or without thrombosis, was found in only 12 instances, eleven of these occurring in men. The total number of patients in both the high and low blood-pressure groups who presented definite clinical or pathological changes relative to the cardiovascular system was 51, or 23.3 per cent. This appears to be low in comparison with the expected figure for the age group of diabetics studied, when tuberculosis is not a factor.

13. Diabetes mellitus was encountered in all degrees of severity. Ketosis, sometimes associated with coma, was often found either as a symptom initiating the onset of the tuberculosis or of an exacerbation of a previously quiescent process. There was no relationship between the severity of the diabetic process and the type of tuberculous disease encountered.

14. Dietetic management was standardized by the use of a basic diet

of 150 gm. carbohydrate, 75 gm. protein, and 100 gm. fat. On this diet it was found that glycosuria could be readily controlled by the addition of insulin, and that the patients gained from 2 to 4 lbs. weekly. No necessity could be established either for the use of the individual weighed diet or for heroic additions to the carbohydrate given.

15. Insulin was used solely with the object of improving the nutrition of the patient, and its dosage was governed by the patient's ability to utilize the standard diet. Large gains in weight and strength were found to be the rule, even when fever was present. Insulin was given after meals and never in a single dose larger than 40 units, in order to prevent attacks of hypoglycemia. There was no causal relationship between the administration of insulin and either the development or the reactivation of the pulmonary tuberculosis. Insulin cannot convert an exudative lesion in the tuberculous diabetic into a relatively benign one.

16. Of the 218 patients, 159, or 72.9 per cent, are dead. Twenty-six patients could not be traced. Thirty-three, or 15.1 per cent, are alive. Nine had always had minimal fibrotic tuberculosis. Of the remaining 24 patients with active tuberculosis, 12 are seriously ill with their pulmonary disease, 5 are in a quiescent state without pneumothorax treatment, and 7 are clinically well following collapse therapy.

14. CONCLUSIONS

From an analysis of these 218 cases in which pulmonary tuberculosis and diabetes mellitus coexisted, we can establish certain features of the natural history of these diseases. The prognosis of the diabetic in whom tuberculosis manifests itself is very serious with a staggeringly large mortality in a relatively short time. This occurs despite the proper management of both diseases. Diet and insulin therapy apparently play no part other than assisting the general body nutrition, either in ameliorating the tuberculous process or bringing about exacerbations. Only therapeutic pneumothorax, when successful, seems to check the steady progress of the active tuberculous process.

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DIABETES AND TUBERCULOSIS

II. Detailed Reports of This Combination of Diseases[1]

GORDON B. MYERS AND RICHARD M. McKEAN

Between August 1, 1929 and April 1, 1934, 80 cases of diabetic tuberculosis were under observation at Herman Kiefer Hospital, Detroit. Statistical studies of the entire group have been published recently (1), (2). The method of treatment of both diseases is discussed at length there. In this communication 8 cases are reported which illustrate points brought out in the analyses.

CASES

1: H. Z., white female, age 14. (*Example of an excellent response of a far-advanced mixed tuberculosis in a severe diabetic to insulin and bed-rest.*) *P. I.:* The patient gave a history of an abrupt onset of polydipsia, polyuria, polyphagia and weakness in November, 1925, at the age of 10, leading to coma within 2 weeks. During the next 3½ years she was admitted to a general hospital five times in severe acidosis. From January to March, 1927, she had a scantily productive hacking cough, a dry pleurisy and frequent night-sweats. These cleared up spontaneously and she was relatively free from pulmonary symptoms for the next two years. In December, 1927, an ischio-rectal abscess was surgically drained. In February, 1929, the cough, pleurisy and night-sweats returned. One month later, a positive diagnosis of tuberculosis was made by X-ray and sputum examinations. No history of haemoptysis. *F. H.:* Father has diabetes. No history of tuberculosis. *P. E.:* Negative except for the chest. The roentgenogram revealed scattered exudative infiltrations throughout both lungs with a cavity at the right apex. *Course in hospital:* The patient was under sanatorium care for about 40 months. Though she received no form of surgical collapse, the cavity closed and the infiltrations on both sides underwent gradual absorption. During the last year in the hospital the patient was asymptomatic and her sputum consistently negative. At discharge her left lung was fairly clear and the few remaining infiltrations on the right were well defined. During the last 12½ months of hospitalization she received a diet consisting of 70 gm. carbohydrate, 50 gm. protein and 150 gm. fat daily. Though this diet furnished but 1,830 calories, the patient gained

[1] From the Tuberculosis Unit of the Herman Kiefer Hospital, Detroit, and the Department of Internal Medicine, Wayne University.

a total of 8.9 kg. (19.5 lbs.). In view of the special precautions to prevent cheating (as described in previous papers), we believe that this patient obtained no additional food. From 55 to 65 units of insulin were required daily. Since the diet contained only 114 gm. available glucose, the patient was almost a total diabetic. The diabetes was best controlled when nearly half of the total daily dose of insulin (26–32 units) was given at 2 A.M. and the remainder in small amounts before each meal. *Course since discharge:* During the three years that have elapsed since her discharge the patient has been active at home, doing her own housework, and has been entirely free of symptoms. The last roentgenogram, taken in January, 1935, showed only a few well-defined infiltrations in the right infraclavicular region and a small amount of fibrosis at the left apex, and was classified as disclosing an arrested minimal lesion. The patient has had hyperglycaemia and glycosuria frequently since discharge but has not been in acidosis and has been free of diabetic symptoms.

Comment

According to Root (3), the severe juvenile diabetic, who is poorly controlled and is frequently in acidosis, is particularly liable to develop tuberculosis. It is probable that the cough and pleurisy in the winter of 1927 represented the initial infection in case 1. If tuberculosis had been suspected at that time and if the patient had been treated accordingly, the exacerbation two years later and the long period of hospitalization might have been averted.

With the advent of her tuberculosis, the insulin requirement rose from 30 to 85 units daily. After the diabetes was brought under control in the sanatorium, the insulin requirement fell to between 55 and 65 units daily. Afterward, the carbohydrate tolerance remained unchanged despite progressive improvement in the tuberculosis.

This patient was one of a small minority in our series in whom medical treatment was used exclusively with ultimate results as good as could have been expected from surgical collapse. If collapse therapy had been instituted, it is probable that her hospital course would have been shortened.

She must be kept under periodic observation for the remainder of her life because of the possibility of an exacerbation in the tuberculosis. From her course, thus far, it would seem that the chances of a relapse are remote so long as she continues on her present regimen.

2: A. Ed., white male, age 52. (*Example of an excellent response of an extensive mixed tuberculosis to pneumothorax with a parallel improvement in carbohydrate tolerance.*) *P. I.:* The patient was perfectly well until the autumn of 1931.

During the fall and winter of 1931–1932 he noted a progressive loss of strength and weight, amounting to 30 lbs., despite a good appetite. This was accompanied by polydipsia and polyuria. In addition, the patient had a persistent cough, productive of a small amount of occasionally blood-streaked mucus. He had pleurisy. *F. H.:* Four siblings died of tuberculosis: no history of diabetes. *P. E.:* On admission (March 26, 1932), the findings were entirely negative except for the chest. There were physical signs and roentgenographic evidence of dense infiltrations of the mixed type throughout almost the entire left lung, with a cavity, 5 cm. in diameter, in the infraclavicular region. There were scattered infiltrations near the middle of the right lung, and an indistinct area of rarefaction at the 2nd interspace. The sputum was positive. *Course in hospital:* With induced pneumothorax, a 50 per cent collapse of the left lung was maintained. The sputum soon became negative the constitutional symptoms rapidly cleared and the cavity finally closed. The infiltrations on the right underwent partial absorption and the area of rarefaction disappeared. Fifty units of insulin daily were required to bring the blood-sugar down to normal, following which, carbohydrate tolerance steadily improved parallel with the tuberculosis and, prior to discharge, the patient was well controlled on 5 units daily. His weight remained constant while on a 2,260 calory diet consisting of 100 gm. carbohydrate, 60 gm. protein and 180 gm. fat, but it increased steadily after the fat intake was raised to 210 gm. daily. *Course since discharge:* Left phrenic crushing was done on April 6, 1933, one week before the patient left the hospital. Since his discharge he has returned to his old job as a travelling salesman and has remained symptom-free. His diabetes has been well controlled on 5 units of insulin daily. He has received pneumothorax refills at regular intervals and, in his last roentgenogram taken on May 31, 1934, the pulmonary process showed further retrogression. His work has taken him away from Detroit and he has not been heard from since then. His future depends greatly upon his faithfulness to his diabetic regimen.

Comment

In more than one-half of our cases the tuberculosis became clinically manifest after the age of forty. The older patients, as a group, responded better than the younger ones, possibly because the diabetes was less severe and the tuberculosis less fulminating.

3: F. Lu., white male, age 48. (*Example of a relapse of an apparently arrested tuberculosis concurrent with gross neglect of the associated diabetes.*) *P. I.:* The patient was not aware that he had diabetes and gave no history of diabetic symptoms. For 5 months preceding admission he had had a scantily productive cough and had raised blood-streaked sputum on two occasions. There had been no pleurisy. He had had intermittent night sweats during the month

prior to entry. Any weight loss was indeterminable. *F. H.:* Negative. *P. E.:* Was negative on admission April 4, 1930 except for the lungs. The roentgenogram revealed dense infiltrations of the mixed type throughout the upper half of the right lung with a cavity, 2 cm. in diameter, at the 2nd interspace. There were scattered productive infiltrations below the left midlung. The sputum was repeatedly positive. *Course in hospital:* With pneumothorax, a partial collapse of the right lung was obtained, following which the sputum became negative and the cavity closed. The pneumothorax was complicated by a massive pleural effusion which necessitated a marked increase in insulin dosage. As the effusion diminished, a gradual absorption of the parenchymal lesions on both sides occurred, accompanied by a parallel improvement in carbohydrate tolerance. The insulin required for diabetic control fell gradually from a peak of 79 units daily during the height of the effusion to 6 units daily toward the end of the patient's stay in the hospital. At discharge, exactly 3 years after admission, there were a few well-defined productive lesions above the 3rd rib on the right, whereas the left lung was clear throughout. The patient had been up and about the hospital for more than a year, symptom-free and considered an apparently arrested case. *Course since discharge:* After leaving the hospital on April 11, 1933, he disappeared from observation and was not heard from for nearly a year. He returned on March 22, 1934, with fresh exudative lesions in the middle third of the right lung and infraclavicular region of the left lung, and a cavity at the 2nd interspace on the left. He had lost 9 kg. and had had a recurrence of pulmonary symptoms. The sputum was again positive. Thirty-five units of insulin were required daily to bring his blood sugar down to normal. The carbohydrate tolerance did not improve during his second term in the hospital, and the insulin could not be reduced further without hyperglycaemia. Owing to adhesions, an artificial pneumothorax could not be established on either side. Following a right phrenic crushing the sputum became negative, and the patient again symptom-free, regaining all of his lost weight. According to the last roentgenogram (June, 1935) the infiltrations on the right had undergone fibrosis while those on the left showed considerable absorption. The cavity was no longer visible. The patient was discharged on August 2, 1935. Arrangements were made for his adequate supervision in the hope of preventing a second relapse.

Comment

Whereas carbohydrate tolerance is often unaffected by an exacerbation in parenchymal tuberculosis, it is usually, as in this case, made worse by the development of a tuberculous pleural effusion.

During the latter part of the patient's first hospital stay it was found that the blood-sugar remained within normal limits on a diet providing

151 gm. available glucose when 6 units of insulin were given daily, but rose to between 180 and 220 mgm. per cent when the insulin was discontinued. However, after leaving the hospital, the patient disappeared from observation, stopped taking insulin and ate everything he pleased. We believe that the gross neglect of the diabetes was chiefly responsible for the relapse in the tuberculosis and wish to emphasize the necessity of careful life-long diabetic control.

4: A. K., housewife, aged 56. (*Example of an excellent response of exudative tuberculosis to bed-rest and phrenicectomy despite a rather poorly controlled diabetes and progressive fall in carbohydrate tolerance.*) *P. I.:* Two years before admission the patient was told that she had diabetes. One and one-half years ago, out of a clear sky, she raised about a pint of blood. She had no further symptoms until May, 1930, one year before entry, when she began to have a scantily productive cough and pleuritic pain in the right side. In September she had another severe haemoptysis followed by blood-tinged sputum. Her weight-loss in two years totalled 50 lbs. She had no history of fever or night-sweats. *F. H.:* Father died of tuberculosis. No history of diabetes. *P. E.:* Entirely negative on admission (April 28, 1931) except for the lungs. There were physical signs and roentgenographic evidence of consolidation of the upper third of the right lung, with several cavities, the largest 5 cm. in diameter. There were scattered infiltrations of mixed type in the middle third of the left lung. The sputum was positive for tubercle bacilli. *Course in hospital:* The diabetes was brought under fair control in June, 1931, by 24 units of insulin on a diet containing 117 gm. available glucose. During the remainder of the patient's hospital stay the blood-sugar was generally between 150 and 200, though the urine was, with but few exceptions, sugar-free. A steady increase in insulin dosage was necessary, because of the persistent hyperglycaemia and, one year later, 71 units were required on a diet containing 135 gm. available glucose. No intercurrent disease was detected to account for the increasing insulin needs. Despite the poorly controlled diabetes, the tuberculosis gradually improved. Pneumothorax was unsuccessful because of adhesions. After phrenicectomy a good collapse was obtained, the sputum became negative, the cavities closed, the infiltrations underwent considerable absorption; and the patient became symptom-free and gained 12.9 kg. (28.3 lbs.) during one year on a diet furnishing only 2,020 calories. She was discharged on August 13, 1932. *Course since discharge:* The patient led a sedentary life, and was asymptomatic and, for the most part, sugar-free on the same diet with 58 units of insulin daily. When she was last examined on April 19, 1934, twenty months after discharge, the roentgenogram showed a few sharply outlined productive lesions in the upper third of the right and at the apex of the left lung. One month later she was killed in an automobile accident.

Comment

A high caloric diet is usually prescribed for patients with pulmonary tuberculosis. The average diet served to nondiabetics in the Tuberculosis Unit of Herman Kiefer Hospital contains 2,800 calories. However, cases 1, 4 and 5 gained considerable weight and showed concurrent improvement in the pulmonary lesion during the course of a year on diets furnishing 1,800 to 2,100 calories daily. Forced feeding in excess of bodily needs increases pulmonary ventilation and is thus inconsistent with the principle of rest that underlies the treatment of tuberculosis.

In our comments on case 3 we emphasized the necessity of keeping the diabetes under control in order to minimize the tendency toward relapse in the tuberculosis. The question arises as to whether it is necessary to keep the blood-sugar constantly within normal limits or whether it is sufficient to prevent glycosuria and acidosis, and therefore permissible to disregard mild hyperglycaemia. If the latter proves sufficient, management in the home will be greatly simplified. In case 4 the tuberculosis improved steadily even though the diabetes was only controlled well enough to avoid glycosuria and acidosis. Fourteen similarly controlled cases have been under observation at home for from one to three years with but one instance of relapse to date. Much more extensive experience will be necessary to determine whether constant maintenance of the blood-sugar within normal limits is indispensable for the best results. One is meanwhile probably justified in depending entirely on urine examinations when frequent blood-sugar determinations are inconvenient.

5: L. S., colored female, aged 24. (*Example of eventual closure of a solitary apical cavity following phrenicectomy and tuberculous empyema after pneumothorax had failed.*) *P. I.:* Began 6 months before admission with loss of weight and night-sweats, when the patient was told that she had diabetes. For four months she had had a scantily productive cough, but never a haemoptysis or pleurisy. *F. H.:* Sister died of tuberculosis in April, 1930. No history of diabetes. *P. E.:* Entirely negative, including the chest, on admission (October 14, 1930). In the roentgenogram, was a cavity, 5 cm. in diameter, at the 2nd left interspace. The right lung was clear. The sputum was positive for tubercle bacilli. *Course in hospital:* With pneumothorax, a good collapse of the left upper lobe was obtained, but the cavity was not reduced in size. Phrenicectomy was done on May 1, 1931. Soon afterward, a tuberculous empyema developed, but the cavity closed, the sputum became negative and and the carbohydrate tolerance steadily improved. This patient maintained

her weight at a constant level for 205 days, on a diet containing 1,840 calories (carbohydrate 95 gm., protein 50 gm., fat 140 gm.), but she gained a total of 12 kg. (26.4 lbs.) in 336 days on a diet containing 2,100 calories (carbohydrate 70 gm., protein 50 gm., fat 180 gm.). The tuberculosis improved more rapidly on the high fat regimen, but this, of course, may have been a matter of coincidence rather than of cause and effect. At the patient's discharge (April 30, 1932), the pleural fluid was almost gone, the patient was asymptomatic, and the diabetes well controlled without insulin. She did not follow her diet at home and, on her return six months later with an encapsulated empyema, the same amount of insulin (45 units daily) was needed to bring the blood-sugar down to normal, as on her first admission. With drainage and merthiolate instillation, the encapsulated empyema gradually disappeared and the carbohydrate tolerance showed parallel improvement. *Course since discharge:* Since her final discharge (June 14, 1933) the patient has done her housework and has been asymptomatic. She has not adhered closely to her diet and has shown intermittent glycosuria, but has been free of acidosis. The last roentgenogram on July 15, 1935 showed pleural thickening and adhesions on the left with retraction of heart and trachea to left, but no cavities or pleural fluid. The right lung was clear.

Comment

This is one of the few advanced cases of diabetic tuberculosis that we have encountered in which symptoms and physical signs were not sufficiently suggestive to permit a correct clinical diagnosis.

In April, 1931, while in the hospital, the parenchymatous process spread and, for a period of 32 days, the patient ran a continuous fever averaging 100.2° in the morning and 101° in the afternoon. Since the diabetes was under good control beforehand, an opportunity was afforded for observing the effect of a flare-up of her tuberculosis upon the carbohydrate tolerance. The diabetes remained under control throughout the entire febrile period on the same diet and insulin dosage as given when the patient was afebrile. In this instance, therefore, the exacerbation of tuberculosis had no effect upon carbohydrate tolerance. With a pyogenic infection of like severity, the insulin needs would probably have been doubled or trebled. Since leucocytes are thought to contain an insulin neutralizing substance, the difference in the effect of tuberculous and pyogenic infection upon carbohydrate tolerance may be due, in part, to the difference in the leucocytic reaction provoked.

6: D. G., white female, aged 25. (*Example of a unilateral productive tuberculosis which spread to the opposite lung on two occasions, undergoing complete*

resolution spontaneously the first time and fibrosis with the aid of bilateral pneumothorax the second time.) *P. I.:* Patient had had diabetes for four years prior to entrance. Otherwise in good health until Christmas, 1930, when taken ill with a scantily productive cough, pleuritic pain in left chest and frequent night-sweats, all of which persisted until admission to hospital two months later: no haemoptysis. *F. H.:* Negative. *P. E.:* On admission (February 27, 1931) negative except for lungs. The roentgenogram revealed scattered productive infiltrations in the upper half of the left lung and several cavities near the clavicle, the largest 4 cm. in diameter. The right lung was clear. *Course in hospital:* Left pneumothorax was induced and, though complicated by pleural effusion, it eventually led to closure of the cavities. Meanwhile, exudative lesions appeared on the right, accompanied by transient hyperglycaemia. These disappeared completely after the cavities on the left had closed. Toward the end of her first hospital stay the patient showed marked hyperglycaemia for no obvious reason except that she was very homesick. She left on October 11, 1932, against advice, did not follow her diet rigidly at home, and returned three months later with fresh mixed infiltrations and a 2.5-cm. cavity in the right upper lobe. Sputum was positive. A 70 per cent pneumothorax was maintained on the left and a 15 per cent pneumothorax induced on the right side, resulting in closure of the cavity and partial absorption of the infiltrations in the right upper lobe. Except for a tuberculous pleural effusion which cleared completely within six months, no change was detected in the left lung during her second admission. Her last roentgenogram, taken in July, 1935, showed circumscribed fibrosis at the site of the former cavity in the right infraclavicular region. The left lung was well collapsed. No cavities were visible, but there was still a small amount of pleural fluid. The sputum had been consistently negative since April, 1933. The patient was symptom-free and awaiting discharge in the autumn of 1935. She was kept in the hospital longer than is customary in the hope of preventing further spread of the infection to the right lung.

Comment

The above patient had a very labile carbohydrate tolerance and presented a difficult problem in diabetic management. When she was first admitted, the mistake was made of placing her on a high fat diet without insulin. She promptly lapsed into coma, but was revived by large doses of insulin. Coincidently with the spread of the parenchymatous process to the right lung, the blood-sugar rose abruptly, necessitating an increase of 15 units in insulin dosage. The effect of increased activity of the tuberculosis upon the carbohydrate tolerance was, in this case, contrary to that in case 5. Precipitate rises in blood-sugar also occurred

at the onset of both attacks of pleurisy with effusion and accompanied every minor intercurrent infection. The insulin requirement was only increased temporarily each time and, within one to four weeks, fell to the previous level. The average daily dosage was 55 units, divided as follows: 30 units at breakfast, 15 units at supper and 10 units at midnight. From August 30, 1933, the insulin was given fifteen minutes after the meal and from January 6 to September 1, 1934, it was given fifteen minutes beforehand. When the insulin was given after breakfast the 10 A.M. blood-sugar was high (140–180 mgm. per cent) and the 2 P.M. blood-sugar was low (65–105 mgm. per cent). When the insulin was given before breakfast, the reverse occurred, the blood-sugar often sinking low enough by 11 A.M. to produce symptoms. The patient had fewer insulin reactions and was better controlled when the insulin was given after the meal.

7: R. H., white female, aged 27. (*Example of poor response of a unilateral mixed tuberculosis to pneumothorax and phrenicectomy with a good result after thoracoplasty.*) *P. I.:* For 6 years prior to entry the patient had had diabetes which was apparently mild but never properly controlled. Since February, 1933, she had had a persistent productive cough with intermittent blood-streaked sputum, night-sweats, and gradual loss of weight and strength. One week prior to admission she had a frank haemoptysis. She had had no pleurisy. *F. H.:* Mother died of miliary tuberculosis. Three siblings have diabetes, one of them tuberculous as well. *P. E.:* On admission (June 17, 1933) negative except for lungs. There were physical signs and roentgenographic evidence of scattered infiltrations of mixed type throughout the upper two-thirds of the left lung with a questionable cavity at the apex. The right lung was clear. *Course in hospital:* Pneumothorax was induced promptly, but, due to apical adhesions, only a partial collapse was obtained. Phrenicectomy was done one and a half months later, resulting in a markedly elevated diaphragm. However, the left lung showed increasing excavation, the sputum remained positive, the constitutional symptoms persisted, and the carbohydrate tolerance gradually declined. Because of the failure of bed-rest, pneumothorax and phrenicectomy, after a five-month trial, thoracoplasty was decided upon. It was done in two stages, the first on December 7, 1933, and the second on January 16, 1934. The postoperative reaction was no more severe than in the nondiabetic. The diabetes was controlled more promptly after the second operation, owing to the use of 50 gm. glucose intravenously and 25 units of insulin subcutaneously every four hours on the day of operation. Following the thoracoplasty, the cavities closed, the sputum became negative, the constitutional symptoms disappeared, and the carbohydrate

tolerance rose to its preoperative level. After six months had elapsed without any symptoms, signs or roentgenographic evidence of recurrence, graded activity was begun. This was so well tolerated that it was difficult to keep the patient from doing too much. She demanded her discharge from the hospital on October 1, 1934. *Course since discharge:* The patient has done her own housework, but has not as yet returned to her former job. She has remained symptom-free and her sputum has been consistently negative. Her last roentgenogram on August 23, 1935, showed good surgical collapse of the left lung without cavitation. The right lung was clear.

Comment

Prior to the thoracoplasty her course was steadily downhill and her outlook was very gloomy. Following the operation, the cavities closed, the sputum became negative and the patient became symptom-free. The tuberculosis is at present apparently arrested. In this case, we believe that the thoracoplasty was life-saving.

8: L. J., colored female, aged 45. (*Example of a progressive downhill course in the tuberculosis accompanied by a steady improvement in carbohydrate tolerance.*) *P. I.:* The patient was perfectly well until February, 1933, when she began to cough, raising blood-streaked sputum. In March, she developed pleurisy on the right side. During the month prior to admission she lost weight and strength rapidly and had severe night-sweats. The diabetes was discovered after admission to the hospital. *F. H.:* Two sisters died of tuberculosis: no history of diabetes. *P. E.:* On admission (April 20, 1933) negative except for chest. There were physical signs and roentgenographic evidence of exudative consolidation of the right infraclavicular region with a 2.5-cm. cavity. The left lung was clear. *Course in hospital:* During the first two months there was little change in the patient's tuberculosis. At that time it was difficult to control the diabetes, even with large doses of insulin. In spite of a 75 per cent collapse by artificial pneumothorax, the tuberculosis began to spread, and by October, 1933, it was so extensive that pneumothorax had to be discontinued because of dyspnoea. The patient's course from September 1, 1933 to her death on May 16, 1934 was one of increasing pulmonary involvement and increasing toxaemia. During this period, her carbohydrate tolerance, as judged by the fall in insulin requirements from 48 to 6 units daily on a uniform intake of available glucose, showed progressive improvement.

Comment

This is an example of the rapidly spreading excavating pneumonic form of tuberculosis as it is encountered particularly in the colored race.

It is possible that early thoracoplasty might have checked the spread of the tuberculosis, as in case 7. The apparent improvement in carbohydrate tolerance while the tuberculosis was extending was probably due, in part at least, to undernutrition.

SUMMARY

1. Eight cases of associated diabetes and tuberculosis have been reported.

2. Five of those illustrate the apparent arrest of far-advanced pulmonary lesions under bed-rest and careful diabetic control alone and when supplemented by artificial pneumothorax and phrenic-nerve surgery.

3. Two instances of the complete failure of such therapy have been cited. In one of these, the pulmonary process was apparently arrested subsequently by thoracoplasty.

4. One case has been reported to exemplify the relapse of an apparently arrested tuberculosis concurrent with gross neglect of the associated diabetes.

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INSULIN AND TUBERCULOSIS

A Partial Review of the Literature and Bibliography

FREDERICK M. ALLEN

The writer (1) was the first to publish a report of the use of insulin in tuberculosis, among the earliest cases of diabetes receiving insulin treatment. The striking improvement observed subsequently in many of these cases complicated with diabetes gave encouragement for the trial of insulin in nondiabetic tuberculous cases. This undertaking was made possible through the collaboration of two groups of tuberculosis specialists, one in New Jersey and the other in New York, who provided the requisite basis of knowledge and skill for the general management and study of the cases. The general trend of the literature at that time (1931) was unfavorable to such treatment of nondiabetic cases; most tuberculosis specialists were unacquainted with the method, and it was not in practical use in the leading institutions. Although there has since been a considerable growth of knowledge and approval of the method, the literature and history are still not generally familiar and no comprehensive review is available. The following bibliography is necessarily incomplete, owing to the great extent of the literature. Many additional references are furnished by the authors here cited. The literature on tuberculosis combined with diabetes is omitted altogether. The only attempt of this partial review is to give a fair representation of the development and status of the subject, for such persons as may be interested in a general conspectus of this character.

It seems convenient to subdivide the topic as follows:

A: General metabolic considerations
1. The blood-sugar and carbohydrate metabolism in tuberculosis
2. Special conditions affecting the blood-sugar in tuberculosis
3. Interrelations of tuberculosis and diabetes
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B: Insulin therapy of nondiabetics
1. Insulin in simple undernutrition
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A. GENERAL METABOLIC CONSIDERATIONS

1. The Blood-Sugar and Carbohydrate Metabolism in Tuberculosis

Observations (mostly incidental to other studies) by many authors indicate that the fasting blood-sugar in tuberculosis is typically normal, with occasional slight deviations either up or down. McBrayer in 1921 made a detailed investigation of the blood-sugar in 74 tuberculosis cases, together with basal-metabolism determinations. He reported the blood-sugar elevated in 58 per cent, normal in 27 per cent and decreased in 16 per cent. Among 46 moderately or far-advanced cases, 65 per cent had increased, 28 per cent normal, and 7 per cent decreased blood-sugar. It must be noticed that "all blood was collected from $1\frac{1}{2}$ to 4 hours after a breakfast light in carbohydrate," and 0.08 per cent was fixed as the normal figure; also the use of the Epstein method precluded the most precise accuracy. The results do not give the impression of any significant disturbances.

The carbohydrate metabolism in tuberculosis has been further investigated by many glucose-tolerance tests.

Langston found hyperglycaemic curves after 100 gm. glucose not only with carcinoma but also with tuberculosis. The levels were typically high with jaundice. Among 29 tuberculosis cases, 20 showed blood-sugar rising to near 200 mgm. in 45 minutes and nearly equalling or even exceeding this figure after two hours. This reaction occurred in three of 6 cases of incipient tuberculosis; one of these persons was supposed to be normal until the finding of this hyperglycaemic curve led to a physical examination, and a few weeks later the sputum contained numerous bacilli.

Seitz described hyperglycaemia in nondiabetics with staphylococcal infection. In tuberculosis the fasting blood-sugars were all normal, 60 to 75 mgm., and after glucose administration the maximum was not above 126 mgm. except in three cases, in which it rose to 148, 150 and 217 mgm., respectively.

Bonnonno refers to a number of Italian investigators, some of whom described the carbohydrate metabolism in tuberculosis as normal, while a larger number found abnormalities. He administered 50 gm. glucose to 25 patients, fasting. In cases of first-stage tuberculosis the blood-sugar, from a fasting level of 90 mgm., rose to a maximum of 130, and within two hours fell to 72. Cases in the second stage of tuberculosis showed the same average fasting level of 90 mgm., but the blood-sugar after one hour was 152 and after two hours 116 mgm. The curves in

third-stage tuberculosis were parallel to those in the second stage, but higher. From a fasting average of 100 mgm. the sugar reached a maximum of 170 mgm. and after two hours it was 135 mgm. A miliary case, though recent, imitated the third-stage type of curve, with blood-sugar of 120 mgm. fasting, 220 mgm. maximum, and 180 mgm. after two hours. Two cases of tuberculous meningitis were distinguished by low curves, with fasting blood-sugars of 65 to 68 mgm. and a rise only to 98 or 120 mgm. maximum. In view of the frequency of liver lesions, the author suggests the interpretation that a lowering of carbohydrate assimilation occurs only in severe cases in which the tuberculosis toxin has impaired hepatic function.

Landau and Glogauer standardized their cases by fifteen hours of carbohydrate abstinence and one hour of bed-rest, then fed 20 gm. glucose and determined the blood-sugar every twenty minutes for two hours. They drew the following conclusions: (1) the fasting blood-sugar in tuberculosis cases is within normal limits; (2) using the test with 20 gm. glucose, alimentary hyperglycaemia (130–140 mgm.) is found prolonged beyond normal limits only in occasional severe cases; (3) in mild tuberculosis muscular work, performed by pulling weights while in bed, makes no change in the sugar curve after 20 gm. glucose, but in severe tuberculosis there are two forms of response, namely (a) delayed rise of the curve and prolongation of hyperglycaemia, attributed to asphyxia in connection with the reduced lung area and dyspnoea on exertion, and (b) a lower curve and quicker fall, due to poverty of liver glycogen. In support of their interpretation that this occasional disturbance of carbohydrate metabolism is due to liver impairment, they state that although chromocholoscopy and levulose give no clear results, quantitative urobilin tests indicate hepatic disturbance in a large proportion of cases.

Monceaux in a monograph on metabolic disturbances in tuberculosis made no mention of carbohydrate abnormalities. In a separate paper he found the carbohydrate metabolism normal in tuberculosis patients, because only 5 per cent of them showed glycosuria after ingesting 100 gm. glucose and only 22 per cent after 150 gm. The intramuscular injection of 10 gm. of glucose caused glycosuria in 98 per cent of far-advanced cachetic cases, but not in others. The administration of levulose in the form of honey elicited nothing abnormal.

Martin and Craig gave 80 gm. glucose as an intentionally large dose to tuberculous children. Rising from initial levels of 105 to 145 mgm. (Folin-Wu), the blood-sugars in different cases after half an hour were

144 to 488, after one hour 142 to 375, and after two hours 111 to 184 mgm. Though the high initial values may be explained by the proximity of a meal, the highest curves clearly represent abnormalities.

Rabuchin found the fasting blood-sugar usually normal in tuberculosis, but in the far-advanced cases there was hypoglycaemia below 80 mgm. per cent. On the other hand, the curve of hyperglycaemia following glucose ingestion was often higher and longer than normal. Adrenalin hyperglycaemia was increased in the milder stages, and diminished in the later stages of clinical tuberculosis. Experimentally, rabbits and guinea pigs infected with various types and doses of tubercle bacilli showed at first hypoglycaemia, but in the later stages transitory hyperglycaemia and glycosuria. Tolerance tests with glucose resulted in exaggerated hyperglycaemia, while the effect of adrenalin was less than normal. The liver glycogen was found greatly diminished. The findings were explained as due to dysfunction of the liver, adrenals and sometimes the pancreas. The disturbance of carbohydrate metabolism was considered to furnish justification for the therapeutic use of insulin.

2. Special Conditions Affecting the Blood-Sugar in Tuberculosis

Mention was made above of Bonnonno's observations of low blood-sugar in tuberculous meningitis. Concerning another complication, namely tuberculosis of the adrenals, there is limited information in the report of Olmsted and Gay, who determined the blood-sugar curve after ingestion of 0.8 gm. glucose per pound of weight. "Two cases have been followed for several months. The first patient had tuberculosis of the lungs and gave a normal curve. The second patient, the pathology of whose suprarenal was unknown, gave a subnormal curve. The first case shows the effect of the bacterial intoxication as well as the deficiency of medullary-adrenal secretion."

It is not feasible here to follow the extensive ramifications of the literature pertaining to possible direct influences of the infection on carbohydrate metabolism, especially under the heads of fever, intoxication, and reduction of lung-volume. An extensive literature proves that the glucose tolerance is commonly reduced in acute and chronic "toxic" states, and therefore the difficulty in tuberculosis may lie not so much in explaining the occasional reductions of this kind as the variations.

The hyperglycaemia of ordinary lobar pneumonia has long been familiar. Brugi, another of the Italians whose work in this field is not sufficiently appreciated, referred to the early observations of this kind, and

carried out an admirable investigation of the blood-sugar of pneumonia cases from the first to the thirtieth day. He made comparative tests in the successive stages, by giving 50 gm. glucose and following the blood-sugar half-hourly until the curve fell to normal. He found the hyperglycaemia (in the sense of both height and duration) to be roughly parallel with the temperature, increasing up to the crisis, and often above 200 or 300 mgm. at the maximum. The sudden subsidence of fever and intoxication with the crisis was not accompanied by a corresponding transformation in glucose tolerance, but a gradual change toward normal was completed by about the 20th day. Subnormal blood-sugar curves between the 20th and 30th days were interpreted by the author as a refilling of depleted glycogen deposits.

Lucherini quoted statements from Lovaglio that tuberculous patients without fever or cachexia have hyperglycaemia while those with fever and cachexia have hypoglycaemia, and from Sartorelli that tuberculosis develops without any marked change in the blood-sugar, but in afebrile cases there is hyperglycaemia when the nutrition is good and hypoglycaemia when it is poor. Lucherini reported that with artificial pneumothorax the previously normal blood-sugar is rapidly elevated. Although the introduction of 450 to 600 cc. of air is not considered to produce actual asphyxia, the author regards the hyperglycaemia as asphyxial in character. In one instance the establishment of bilateral pneumothorax was attended by a rise of blood-sugar from 103 to 285 mgm.

Hecht sought to examine the specific influence of tuberculous infection by excluding mild or incipient cases and selecting those with advanced and extensive lesions but without high fever or intoxication. None of these patients had fasting blood-sugars as high as the upper limits of normal. In some of them the blood-sugar fell with progress of the tuberculosis, as low as 56 or 43 mgm. Two cases of therapeutic pneumothorax showed a slight fall of the fasting blood-sugar after the operation and no special change later. The ingestion of 20 gm. glucose by hypoglycaemic patients produced no more than a relative hyperglycaemia of 105 to 107 mgm., but in severe cases this elevation was abnormally prolonged. As only one patient had urobilinogenuria, it appeared that there must be other causative factors than injury of the liver. The general conclusion is that hypoglycaemia exists with extensive tuberculosis even when the nutrition is good, and the cause unknown.

Schlapper and Kirchner made the general statement that the blood-

sugar in mild or moderate tuberculosis is within normal limits and in severe cases below normal, but they did not give details.

Berg found with the Bang method that the fasting blood-sugar in 141 tuberculosis cases ranged between 80 and 120 mgm., the higher figures occurring in severe extensive cases, and the general average being 10 per cent above normal. There was never hypoglycaemia. He reported 70 tolerance tests with the administration of 100 gm. glucose. The maximum in the different curves ranged from 131 to 259 mgm. Healed cases showed the lowest figures, cirrhotic ones next, and exudative, severe and febrile cases the highest. Though exceptions appeared in all groups, in general average the height and duration of hyperglycaemia varied with the severity and activity and also with the erythrocyte sedimentation rate. Repetition of the tolerance tests at intervals in the same cases gave unchanged results in the stationary ones, lower curves in the improved ones and higher curves in the progressive ones. Fever was not the governing factor, for, of 52 cases with high curves, 18 were febrile or subfebrile and 34 fully afebrile. Light treatments reduced the hyperglycaemia (as stated also by Martin and Craig). Adrenalin tests in 7 cases showed that patients with alimentary hyperglycaemia do not necessarily have increased adrenalin hyperglycaemia. Autopsies obtained on five of the cases with high sugar-curves showed an apparently normal liver in one and extreme fatty or amyloid changes in the four others. The author suggests that the hyperglycaemia may be due to stimulation of the thyroid, adrenals or other glands.

Hecht and Bonem found no elevation of the fasting blood-sugar in either febrile or afebrile tuberculosis cases. Both urobilinogen and galactose liver tests gave mixed results. They then injected tuberculous sputum into the peritoneum of guinea pigs. Though the animals lost no weight or even gained, at autopsy their average liver glycogens were 0.739 as against 4.215 per cent for normal controls (regardless of the presence or extent of tuberculous lesions in the liver). They concluded that in tuberculosis the glycogen-forming power of the liver is impaired, probably by the intoxication, and, on this account, they considered insulin therapy to be rational.

Bocassini cited a list of Italian observers in support of the statement that the blood-sugar during digestion is elevated in proportion to the severity of the tuberculosis, and the fall to normal is likewise delayed. This disturbance is attributed to the liver, pancreas, and general endocrine balance, as well as to factors such as fever and asphyxia (diminished lung tissue, pneumothorax).

Heaton tested 6 tuberculosis patients with the ingestion of 1.75 gm. of glucose per kg. body weight. The fasting blood-sugars ranged from 94 to 115 mgm. The peaks of the six curves after one hour were, respectively, 187, 215, 375, 165, 136 and 250 mgm. The author suggests that tolerance tests may perhaps serve for recognition of the cases which will respond favorably to insulin.

From this and other literature the impression may be gained that the glucose tolerance is commonly reduced in any states of infection, fever and intoxication; also, that in a debilitating disease like tuberculosis, fasting hypoglycaemia may occur sometimes, with glycogen deficiency, when there is undernutrition or exhaustion and even without obvious loss of weight. Since the glucose-tolerance test has failed so completely for the diagnosis of liver diseases in general, it is difficult to attribute the reduced tolerance in tuberculosis merely to impaired liver function. Authors disagree widely in their findings and in respect to the influence of individual factors of aetiology. The actual cause of the abnormalities and of the variations between different cases remains unknown.

3. Interrelations of Tuberculosis and Diabetes

It is a truism among authors that tuberculosis is a frequent complication of diabetes, but diabetes supervening in the course of a preëxisting tuberculosis is a rarity. It is also common clinical knowledge that with the coexistence of the two diseases, each tends ordinarily to make the other worse, so that the death-rate from this combination formerly was extremely high. The textbooks of Naunyn and Joslin mention exceptional instances in which the onset of tuberculosis has seemed to improve the diabetic condition, so that glycosuria and acidosis subsided and the food tolerance increased. This improvement, interpreted as due to undernutrition, was in fact one of the hints leading to Allen's experiments with therapeutic undernutrition.

As early as 1901 Nebelthau obtained peculiar results in undertaking to test the influence of fever upon diabetes. He injected depancreatized dogs with diphtheria and tetanus toxins and streptococcus broth subcutaneously, and with tubercle bacilli intravenously. He found that the tuberculous fever behaved differently from the others, inasmuch as in several instances the sugar excretion fell markedly, without reduction of the nitrogen output and without diarrhoea.

Clinically, the relations between tuberculosis and diabetes are the subject of a monograph by Gregoraci and of papers by numerous authors.

Observations on the uncommon influence of tuberculosis in apparently ameliorating diabetes are sparse.

Lundberg regarded this influence as a regular one, saying that, as tuberculosis advances, the tolerance for carbohydrate and protein rises, acidosis and various diabetic symptoms are usually absent, and death occurs always from tuberculosis and never from diabetes. By extracting tuberculous tissues he claimed to have obtained an insulin-like substance, which was supposed to be responsible for such effects. He admitted the inharmonious fact that hyperglycaemia persists in tuberculous diabetics, and he explained this by assuming a thyroid stimulation.

Rosenberg recognized that complications, including tuberculosis, generally aggravate diabetes. But he mentioned arteriosclerosis, hepatic cirrhosis, and cancer in mild elderly cases, as complications which may have the opposite influence, and he gave detailed histories of four patients in whom tuberculosis likewise seemed to improve the diabetic condition. He insisted that undernutrition could not be the whole explanation, because the calories were not reduced and in some instances the sudden increase of tolerance was not accompanied by loss of weight. Nevertheless, on the whole, Rosenberg's case-records show considerable losses of weight.

Ahlenstiel adopted Falta's suggestion that the effect of insulin on the blood-sugar should be proportional to the metabolic disturbance, just as a hyperthyroid patient reacts more strongly than a normal person to thyroid extract. He therefore determined the blood-sugar curves following injection of 20 units of insulin in various conditions, including inactive and active tuberculosis. As the cases of active tuberculosis appeared less "sensitive" than the others according to this standard, he concluded that the course of tuberculosis represented a prolonged "hunger action" by virtue of which the pancreatic islands were spared and kept in excellent functional condition.

Borock, Wowsi and Ranzman selected 92 severe tuberculosis cases for finger-blood analyses by the Hagedorn-Jensen method. They found a wide range of fasting blood-sugars, from 40 to 140 mgm. Tests with adrenalin injection likewise had variable results. They concluded that low blood-sugars (40–80 mgm.) belong to cases of poor prognosis and the higher figures (80–140 mgm.) to cases of better prognosis. The lack of parallelism between the blood-sugar and the body-weight seemed to exclude undernutrition as the explanation of the low figures. Liver lesions were also rejected, because in all sorts of liver diseases the blood-

sugar is typically normal. Along with pluriglandular speculations, the authors stress the alleged demonstration by Kasarnowskaja that the islands of Langerhans become hypertrophic in long-standing chronic tuberculosis. The degree and duration of the intoxication, not the extent of the lesions, are supposed to govern this effect.

Without going into the literature on this topic further, it may be suggested as rather surprising that so many authors have sought the causes of altered carbohydrate metabolism in the liver and other organs rather than the pancreas. There exists no real proof of an influence of tuberculosis upon the pancreatic islands, and especially the requirements for demonstrating either increase or reduction of the Langerhans tissue have never been fulfilled, but there may be some interest in closer observations on this, a point which has been almost ignored by pathologists. There is also a theoretical possibility that some latent diabetics (such as persons who have a subnormal assimilation tending to produce latent or outright diabetes, but in whom the tendency has been suppressed by the nutritive injury of tuberculosis) are included among the large tuberculous population, but this explanation could serve only for a limited number or kind of abnormalities and could not be made to cover too large a proportion of patients.

The combination of tuberculosis and diabetes appears to furnish a definite basis for two conclusions of practical clinical value. First, inasmuch as diabetes does not offer immunity against focal or general reactions or against any form of allergic or other injury, the experience in the treatment of the combined diseases sufficiently demonstrates that, with comparatively few exceptions, insulin can be used in tuberculosis cases safely and harmlessly for indefinite periods. Second, it was often possible formerly to abolish glycosuria and hyperglycaemia by limiting diet and weight, and the results thus were actually better than with high diets and uncontrolled diabetes, but nevertheless the combined cases of any marked severity always ended fatally. Insulin, which provides the possibility of normal sugar together with liberal feeding, has revolutionized the results and prognosis. It therefore appears obvious and inescapable either that there is some special value in the insulin itself, or else that nutrition is a more important factor in resistance than some of the opponents of insulin therapy have wished to concede.

4. Effects of Long-Continued Insulin Administration in Nondiabetics

The first clinical investigations in this field were concerned chiefly with the danger of hypoglycaemia. Thus Pitfield gave insulin to maran-

tic infants, even though the blood-sugar in some instances was already as low as 45 mgm. But within four days the blood-sugar in one case was found to have risen to 104 mgm. He refers to the Toronto experience with rabbits, which developed transitory hyperglycaemia after a course of daily insulin injections had been discontinued.

Falta made blood-sugar tests throughout the day to prove that his high insulin dosage (as much as 150 units a day in asthenic nondiabetics) never caused hypoglycaemia if the customary frequent carbohydrate feedings were employed. He and others of the Vienna school also made observations leading to the conclusion that the administration of insulin for a few weeks results in augmented function of the patient's own pancreatic islands. A practical result of this process is that numerous persons fattened with insulin are able to retain this higher weight after the treatment is stopped.

Bauer and Nyiri began their work with experiments to determine the amounts of carbohydrate required to maintain normal blood-sugar in nondiabetics after doses of 5 to 60 units of insulin. Their records include blood-sugar figures up to 170 mgm. Also, with insulin the blood-sugar fell to a minimum of 70 mgm., while without insulin it fell only to 80 mgm. after 20 hours' fasting.

Schellong and Kramer were the first to report tolerance tests during the course of insulin fattening treatments, though their method consisted in administering 75 gm. of cane-sugar. The blood-sugar curves with insulin showed a steeper rise and earlier fall than in the control tests before the use of insulin.

Zelter seems to have been the first to apply these tests to tuberculosis patients receiving insulin (up to 60 units daily). His table shows normal fasting blood-sugars before, during and after the insulin treatment; also the administration of 50 gm. of cane-sugar produced only trivial changes.

Mascher found that the fasting blood-sugars were slightly lower in active tuberculosis cases than in inactive ones. After the termination of treatment, the fasting blood-sugars in patients who had received insulin were lower than in those who had not received it. The author interpreted this observation in favor of the view that weeks of the insulin treatment strengthen the function of the patient's pancreatic islands.

Ager described the treatment of a tuberculous man with 10 to 20 units of insulin per day, with resulting gain of $8\frac{1}{2}$ lbs. in eight weeks. The initial fasting blood-sugar was 80 mgm. About three weeks after beginning insulin, the fasting blood-sugar at 10 A.M. was 90 mgm., and 100 gm. glucose was then given. The blood-sugar at 10:30 was 180 mgm., at

11 it was 210 mgm., and at 11:30 it was 140 mgm. At 11:40, 10 units of insulin were given, and at 3 P.M. the blood-sugar was 100 mgm. Glycosuria remained absent.

The paper of Leggett and Callahan contains, along with its valuable clinical observations, several blood-sugar curves. Four of their insulin-treated tuberculosis cases showed actual glycosuria, which they regarded as an unfavorable sign calling for caution in the treatment.

Paul, Clark and Gibson noticed a rise of blood-sugar after the discontinuance of insulin, and therefore planned observations on five other persons (nondiabetic, nontuberculous). The dosage was begun with 5 units before each meal and gradually increased to as high as 17 or 25 units, t. i. d. Blood-sugar analyses two hours after meals were generally normal, sometimes slightly above normal, but hypoglycaemia was rare. On stopping insulin, all these patients showed hyperglycaemia and 4 actual glycosuria. In three out of these six the glucose tolerance was found reduced. A typical example is that of a woman, aged 34, with anorexia after pleurisy. On June 4, in a test with the ingestion of 50 gm. glucose, the fasting blood-sugar was 87 mgm. and there was a rise in 1 hour to 159 mgm. Insulin was then begun with first 5, then 10 units, t. i. d., until June 18. On that day a repetition of the glucose test gave a rise of blood-sugar in 1 hour to 231 mgm. The insulin was continued, and increased up to 25 units, t. i. d., on July 10. The following day the insulin was omitted and the same glucose test given. From the same fasting level of 87 mgm. the course of the blood-sugar in one-half hour intervals was 208, 231, 253, 176 mgm. The urine contained 0.8 per cent sugar in the first hour and 1.1 per cent in the second hour. With the abandonment of insulin the tolerance curves on July 16 and 19 showed gradual but still incomplete recovery of assimilation. A compensating inhibition of pancreatic-island function during insulin administration and subsequent return toward normal were suggested, with the possibility that more detailed studies might demonstrate a different explanation.

B. INSULIN THERAPY OF NONDIABETICS

1. Insulin in Simple Undernutrition

The first recorded use of insulin for building up nondiabetic patients was by Pitfield in athreptic infants. One such baby, aged 4 months, was given 1 unit daily for 7 days, and gained 16 oz. in 16 days. Another, aged 5 months, receiving 0.5 unit daily for 7 days, gained 15 oz. in the week. Marriott followed up Pitfield's work by giving larger insulin

dosage along with glucose intravenously. Thus his case 5, aged 4 months, received daily glucose intravenously and 2 units of insulin subcutaneously for 6 days without gain of weight, but when the insulin was increased to 15 units mixed with the glucose given intravenously there was a gain of 2 lbs. in 12 days. Likewise, his case 6, aged 2 months, gained 1½ lbs. in 10 days. These children furthermore continued to show improved appetite and gain of weight after stopping the treatment. Barbour learned the method from Marriott, but gave the glucose by mouth instead of by vein, and the insulin subcutaneously. His dosage for children under 2 years was 4 units, t. i. d., and, for those above 2 years, 5 units, t. i. d. He considered the results best when the insulin was pushed to the limit of tolerance, and in this connection made an observation which is instructive also in the treatment of adults, namely, "when that point has been reached the patient shows it in one or more of the following ways: a sudden rise in temperature, loss of appetite, nausea, vomiting."

Buttenwieser presented evidence that in "hydrolabile" children insulin markedly influences the tissue turgor and also promotes gain of flesh. Up to the present a considerable literature has developed on the use of insulin in pediatrics (*cf.* recent paper of Radwin and Brown).

Falta first reported marked gains of appetite and weight in 3 emaciated neurasthenic adults under insulin treatment. The highest daily dosage was 150 units, that is, 30 units five times a day. In a few weeks of treatment the first patient gained 9 kg., the second 6.5 kg. and the third 5.7 kg. Falta here claimed priority on the basis of a suggestion in his 1913 book that the pancreatic-island hormone is concerned in some cases of obesity. Priority, however, is not established by hypothetical suggestions. Experimental and clinical evidence of the relation of the internal pancreatic function with the body-weight and the total caloric intake were published by Allen from 1914 onward. Falta has actually not grasped the facts of the relationship, as shown by his remarks on diabetic treatment following his paper (4), and by his disregard of the fat allowance and body weight in his other works on diabetes. In other papers Falta discussed the mechanism of insulin-fattening and classified the types of emaciation suitable and unsuitable for this treatment. He deserves credit as the first to attract general attention to this method.

In the discussion of Falta's first paper, Bauer and Nyiri mentioned their work, which was carried on simultaneously and which was published shortly afterward. Their investigation began as an attempt to determine

the quantities of carbohydrate required to maintain the blood-sugar unchanged in nondiabetic persons after doses of insulin ranging from 5 units up to 60 or even 100 units. The resulting increases of appetite and weight were such as to suggest this method as a treatment of malnutrition. Their courses of treatment lasted 2 to 4 weeks, and the gains of weight ranged up to a maximum of 8 or 10 kg. The results, indications and contraindications were discussed in a later paper by Bauer.

Also closely following upon Falta's work, Vogt reported gains of weight in marantic infants with 2 or 3 units of insulin per day, and subsequently in adults beginning with 10 or 20 units and increasing to 60, 80 or rarely 100 units per day. The usual course of treatment was 3 weeks, and the stopping of insulin was recommended in refractory cases showing no benefit within 3 or 4 days.

Lublin duplicated Falta's methods and results, and also made observations of the influence of insulin on the respiratory quotient and carbohydrate metabolism. Frank likewise followed and supported Falta. Tillgren, Lundberg, Dahl and Andersen added favorable Scandinavian experiences, with some suggestions of individualization of treatment.

Metz began treatment with 10 units, t. i. d., 30 minutes before meals, and increased 5 units per day up to 20 or 30 units, t. i. d., and thus obtained weight increases of 15 to 25 lbs. He also noticed that "when the weight has reached a definite maximum, insulin loses its influence. This maximum is closely governed by the particular individual's normal weight."

Blotner described one case in which, following Barker's recommendation, a woman gained 24 lbs. in 6 weeks of insulin treatment, with improvement in her neurasthenia. Subsequently he treated 19 patients of varying ages, usually with 10 units of insulin, t. i. d. Gains of weight and tonic effects were reported, along with observations of the nitrogen excretion, blood chemistry, blood counts, etc. Jones, and also Stites and Stites, gave similar descriptions of gains in weight and general condition with moderate insulin dosage.

Nahum and Himwich referred to the demonstrated increase of hunger contractions of the stomach with insulin, and also the gains of weight in rabbits used for testing insulin. They gave their patients 3 units of insulin every 3 hours, increasing gradually to 10 or more units every 3 hours. Their 4 patients gained respectively $22\frac{1}{2}$ lbs. in 28 days, 10 lbs. in 12 days, $12\frac{1}{2}$ lbs. in 23 days, and 15 lbs. in 39 days.

Nichol properly criticized the lack of prolonged follow-ups of patients

fattened with insulin. He gave 5 to 15 units before each meal to patients, mostly of the constitutional asthenic type. There was usually a tonic effect upon the general feeling with gain of weight, but the two were not strictly parallel. For example, one man who gained and held 20 lb. of weight was only partially relieved of weakness, while another experienced the tonic effect, although he gained no weight. Of the series of 63 cases, 13 had been reported in 1927, and 48 had gained 5 to 30 lbs. Of the latter, 23 maintained their gains for 3 months or less, 8 as long as 6 months, 7 for 1 year, 3 for 3 years, 1 for 4 years, and 6 were lost from observation. In this same connection, reference may be made to the papers of DePew, Ginsberg, and Lueders.

Barker began with only 4 units before the 2 principal meals, as a precaution against hypersensitiveness, and increased to 10, 15 or more units 30 minutes before meals, t. i. d. He discussed the classification and various treatments of undernutrition, and, concerning insulin therapy, concluded, "Now, after 6 years' experience with it, I am convinced that it is of very great value."

2. Insulin in Various Ailments

Turning from simple malnutrition to more definite forms of disease, it appears that insulin has been tried in almost every ailment to which humanity is heir. As early as 1923, Cowie, Parsons and Raphael gave it to patients with mental depression, not with an idea of fattening but to correct the supposed "slowness with which glucose is used by depressives." It is unnecessary to follow the subsequent literature of the use of insulin in the insane (Kuppers and Strehl; Appel, Farr and Marshall; Sakel; Carriere; Sharp and Bahr), chiefly those who refuse food, also in drug addicts and the like (Anton and Jacobi, Sakel, Modern, Howard, Herbrand). Along with some benefits there appear to be numerous failures, and it is interesting that antipathy to food, apparently of a purely psychic nature, can be so pronounced that it cannot be overcome with insulin.

Falta remarked that gain of weight with insulin in carcinoma cases is possible but transitory, and benefits in cirrhosis or other icteric diseases are doubtful. He also distinguished two forms of simple emaciation, namely the "asthenic" which responds to insulin, and the "erethistic" which is often refractory because of excessive catabolism. Nevertheless insulin may be helpful together with rest and diet in cases of Basedow's disease.

Richter cited some earlier literature, and added his own observations of gains of weight and other marked benefits from insulin in hyperthyroidism, even of very severe type.

Bauer and Nyiri recommended insulin for the emaciation of asthenia, arteriosclerosis, senility, hyperthyroidism, and convalescence from acute infections. They had failures in cancer cachexia: either the appetite was not improved, or insulin could not be tolerated above 10 or 20 units; and even exceptional patients who tolerated 40 to 100 units per day soon began to lose appetite, their general condition became worse, and insulin had to be stopped. It is also suggested that fattening with insulin might be harmful, in analogy with animal experiments showing that tumor growth is accelerated by overnutrition and retarded by undernutrition.

Subsequently Bauer corroborated the uselessness of insulin with neoplasms, but found favorable possibilities in gastric ulcer, and also in vomiting from other causes. He found only slight gains of weight in hyperthyroid cases and could not confirm the enthusiastic reports of other writers. He also had poor results in the emaciation of senility and arteriosclerosis. He made the valuable suggestion that, in nervousness and certain other ailments, insulin should be begun very gradually: large doses at first may produce only weakness and nausea instead of hunger, and the habit of revulsion against food must be slowly overcome. He very wisely opposed the rule of stopping insulin if no benefits were seen within a few days, and advised rather that the treatment be prolonged if necessary to 10 weeks instead of 3 weeks.

Vogt in general corroborated Falta and Bauer, and among the indications for insulin mentioned certain constitutional deficiencies; also emaciation after severe illness or operation, vomiting in pregnancy and other conditions, and furthermore cases needing local fat deposits to correct visceral ptoses, etc.; also the preoperative preparation of certain patients. He quotes from Gauss the case of a woman with benign ovarian tumor, who was received in such poor condition that operation was impossible, but who improved so markedly with insulin that the operation was successfully accomplished.

References are numerous to the treatment of pregnancy and children's disorders (Ehrenfest; Rau; Higgins and Ostlund); cardiac, thyroid and liver disease (Carriere, Boller, Nichol, Franco, and others too numerous to mention); and gastrointestinal ulcers (Feullade; Cade and Barral; Simmitzky; Goyena; Langeron) with insulin, generally with reported benefit. There is also some literature on its use in eczema (Devoto),

scleroderma (Michaelis; Wahl; marked benefit), and various other skin diseases. Golden and Junkin considered that the healing of leg ulcers was favored in two cases by insulin subcutaneously, and it is unnecessary here to notice other reports of treatment of superficial ulcers, especially by local application of insulin. Diphtheria and other infections (Advier and Rion; Bartle; Kostyal; Gunn; Beck; Natin and da Rin; Begg and Harries) are further examples of a considerable bibliography which might be compiled to cover the range of conditions treated with insulin. Several authors have described methods of desensitization which more or less successfully overcome the allergic difficulties arising from insulin.

3. Insulin in Tuberculosis

This literature seems to fall naturally into three divisions, namely (1) incidental observations of the pioneers in insulin-fattening; (2) a great mass of papers devoted specifically to tuberculosis, mostly between the years 1927 and 1929; and (3) a few communications from 1930 onward.

1: Bauer and Nyiri, the first to use insulin in tuberculosis cases without diabetes, reported gains of weight and strength with inactive infections but failures in all forms of wasting febrile disease (*e.g.*, a case of active renal tuberculosis). Bauer likewise opposed the use of insulin in active or severe tuberculosis. Vogt agreed with this view.

Falta stated that "cases with chronic infectious processes, especially with active tuberculosis, are unsuited for insulin treatment." He mentioned further observations showing benefits in suitable afebrile tuberculosis cases, not in the sense that fattening with insulin affects the tuberculous process, but that improvement of nutrition is in itself highly desirable in many such cases. He and others warned against possible serious consequences of hypoglycaemia.

Frank quoted Gabbe and others as having failed to accomplish benefits with insulin in malignant tumors and in febrile diseases, including tuberculosis. He approved of trying to improve appetite and nutrition with small doses of insulin (10 units twice daily) in tuberculous cases with little or no fever, but even here he warned that dangerous focal reactions may be stirred up.

2: Among writers in 1926, Hofhauser and Schön are distinguished by a remarkably bold position in advance of their time. They selected tuberculosis patients who could not be made to gain, and gave insulin,

10 units in the morning and 7 units in the evening, increasing not beyond 50 units per day. They individualized both the daily dosage and the duration of treatment, from 3 to 8 weeks, sometimes repeated. In defiance of earlier advice, their cases were mostly severe, some actively progressive, a few febrile. With improvement of appetite and strength there were gains of 1.6 to 5 kg. in weight. They particularly denied that insulin is a double-edged weapon, that it causes either general or focal reactions or any other harm, or that any contraindications existed. Again defying the grave warnings of earlier writers regarding haemoptysis, in cases with this complication they merely omitted insulin briefly and then resumed it. The weakness of their contribution is that it was only a brief report of 13 cases, and the more extensive observations promised for a later paper seem never to have been published.

Of other writers in 1926, Bodmer followed Vogt's method and found insulin useful in some quiescent tuberculous cases. Schmidt expressed weighty clinical judgment against the insulin treatment, without details of his own experiences. Böckheler treated a small series of 13 cases, not all tuberculous, with 20 to 60, rarely 90 units of insulin per day, with some gains of weight and some suspected general or focal reactions, ending with scepticism as to the value of the method. Torday reported 6 mild tuberculous cases receiving 30 to 50 units of insulin per day, and concluded that small doses sometimes stimulate appetite and weight but that larger doses may have bad effects. In the discussion of this paper Mandoki testified to gains of 3 to 7 kg. in mild tuberculosis with anorexia, while Schaffler warned that in 2 cases of tuberculosis with diabetes there had been sudden flare-ups of fever and haemoptysis during insulin treatment.

Ahlenstiel and Piel, treating 25 cases, mostly with 20 to 40 units of insulin daily for 2 or 3 weeks, concluded that insulin builds up weight only in a small number of inactive cases; and that in severe or progressive cases it produced no lasting gain of weight but, on the contrary, many rather serious focal reactions.

Dumarest and Theodoresco stated that they were unaware of any prior use of insulin for pulmonary tuberculosis. They avoided serious cases, and gave their 6 afebrile or subfebrile patients 10 to 35 units daily for 2 to 4 weeks. They found some slight gains of weight but were sceptical of its value.

In 1927, Grossfeld published 8 out of "many" cases which he had treated with insulin, following Falta, with doses of 5 to 30 units daily

for 1 or 2 weeks. The weight gains were from 1 to 8.4 kg., and he mentions 4 additional patients with gains up to 7 kg., together with improvement in their pulmonary condition. He considered insulin suitable for fibrotic and stationary cases, not for those with high fever, but he denied that focal reactions are ever produced.

Herich treated 16 cases "of all stages," beginning with 5 units twice daily and increasing 10 units per day to a maximum of 60 units, generally for the usual 3 weeks. The chief gains of weight were in severe cases: two practically well patients and three with slight lesions showed no benefit. The weight gains were all soon lost; the patients considered this improvement deceptive and were unwilling to repeat the treatment. Besides minor inconveniences of hypoglycaemia, there was an open question whether haemoptysis, the onset of intestinal foci, and spontaneous pneumothorax were due to insulin. The author condemned the method as representing no therapeutic advance.

Morin and Bouessée reported 8 cases controlled with long observations in the sanatorium before and afterward. They began insulin with 5 units once a day and increased sometimes as high as 60 units, divided in 2 or 3 doses. One month of such treatment often produced gains of 4 or 5 kg., which were retained or even increased afterward. No harmful effect was ever seen in general or local symptoms. One severe bilateral case at age of 18, with steady loss of weight for a year (and evidently febrile), showed a gain of 4.3 kg. under insulin but a loss to below the former level after insulin was stopped. Schlapper and Kirchner used 10 to 15 units of insulin, t. i. d., in the "large material" of their institution, and drew general conclusions that in mild, afebrile, inactive or only moderately active cases marked gains of appetite and weight can be achieved. The greatest gains were in those of asthenic constitution with active tuberculosis just beginning. In the milder forms of outspokenly active tuberculosis the authors obtained no more gains of weight than is customary without insulin. In severe cases they had complete failures. No bad effects, however, were obtained in respect to either focal or general symptoms.

Grossfeld published records of 8 out of "many" cases in which he used the conventional insulin treatment. Notwithstanding some gains of weight and general improvement he drew no very positive conclusions.

Lepskaja and Rachlin gave insulin to 6 tuberculous women (5 afebrile, 1 almost so). After trial doses of 4 to 8 units they increased slowly to 56, and in one instance to 70 or 80 units per day. The courses lasted 3 to

5 weeks, with omissions of a few days due to the curious idea of many early writers that insulin should not be given during menstruation. There were weight gains of 2 to 5 kg., which persisted or increased during observations of 3 to 6 months after stopping insulin. The fact was noticed that each patient had an individual optimal dose: increases above it retarded rather than assisted improvement. With insulin, diets of 4,000 calories were easily eaten.

Zelter's two papers dealt respectively with 24 and 10 patients who had failed to gain weight during 6 to 8 weeks of regular treatment, but he "naturally" excluded severe and febrile cases. The doses increased gradually from 5 to 60 units per day, and the duration was the usual 3 weeks. There was a moderate weight increase in most but not all cases. Haemoptysis or focal reactions never occurred. Insulin was concluded as being valuable for increasing weight in carefully selected cases of purely productive type, while those with exudative features are to be excluded.

Schönfeld described the treatment of 16 cases, 5 being mild fibrous and 11 cavernous phthisis. With doses of usually 30 units per day, he obtained favorable results in 3 of the former but only 2 of the latter group. In 2 cases there were focal reactions from insulin, but on the other hand 2 severe cases bore insulin well. Schönfeld concluded that the treatment built up weight which is often retained for a considerable time.

In South America, Nario, with insulin doses increasing gradually from 10 to 60 or even 80 units per day, concluded that any slight gains of weight were quickly lost and that the treatment was worthless. In Italy, brief abstracts state the conclusion of Berni that insulin is beneficial in fattening tuberculosis patients not responding to other treatments, and of Andreoni that the method is of dubious value and at best applicable only to a few emaciated nonprogressive cases. A later paper by Turletti is favorable.

Arborelius referred to experiences of only 2 months, including gains of 4 or 5 kg. in quiescent tuberculosis cases during 2 or 3 weeks. Some benefit was found also when exudative processes were early or slight. But in a more pronounced exudative case an injection of only 3 units of insulin caused profound hypoglycaemia passing into convulsions and requiring intravenous glucose to control it.

In 1929 appeared the careful study of Combemale, Gernez and Breton, covering 32 cases under institutional observation for several months or years and followed for 3 to 6 months after insulin treatment. These

cases were selected as having little fever or progressiveness. Of these, 6 retained the entire gain, 5 lost a part, 6 lost all, but 8 gained an additional 3 or 4 kg. after the insulin was stopped. The optimum daily dose was considered to be 30 units, which gave more gain than 15 units. Increased dosage up to 60 units either failed to increase the weight or the increase was not retained. The courses were of various lengths, up to a maximum of 40 days. Repetition of the courses 2, 3 or 4 times gave increased effects, but less in degree than the first course. Harmful effects were attributed to insulin, especially with high or prolonged dosage. These included one fatal haemoptysis and several transitory elevations of temperature, also diarrhoea. Menstruation was never disturbed. Sometimes cough was increased and the sputum became blood-tinged. In one case stationary for 9 months, on the 9th day of treatment with 60 units of insulin and in spite of a gain of 2 kg. weight, there was sudden fever and a turn for the worse, leading to death in one month. In 4 afebrile nonprogressive cases, insulin treatment was followed by a change for the worse, appearance of bacilli in the sputum, and cavitation. The authors therefore advised using insulin only under close watching in carefully selected cases, never in progressive cases or those with unstable temperature. The dosage should not be above 30 units per day and should not be prolonged beyond 2 or 3 weeks. Under suitable conditions the authors favored the use of insulin for improvement of both nutrition and feelings, but study of their tables casts doubt upon the reality or permanence of the benefit. A later paper by Gernez comprised essentially the same features.

Märtensson treated 15 patients with insulin after at least two months of preliminary institutional observation. Active or febrile cases were excluded. The courses lasted about 28 days, beginning with 4 or 5 units and increasing to about 36 units daily. The patients gained up to 4.4 kg., and no focal reactions or other bad effects were noticed. The results and conclusions of Mascher were essentially similar, except that his 18 cases included "all forms and stages" except the most severely febrile and hopeless tuberculosis.

3: In 1930, Ghibellini, stressing the importance of nutrition in tuberculosis, reported 19 cases treated with insulin, increasing from 10 units to 30 units per day. The less severe cases showed gains of weight; the more severe ones, retention of weight with improved appetite. Though the courses were mostly of the traditional 3-weeks duration, they were

sometimes repeated at intervals for as long as 7 months. Mondini sought chiefly to study the protein metabolism by giving insulin for a few days in 4 rapidly progressive juvenile cases, but notwithstanding his findings of improved nitrogen balance, it is obvious that infections of this type cannot be arrested by insulin.

Bocassini followed Falta's ideas and methods. In addition to the weight he made observations of corpuscle sedimentation, leucocyte formula, and urea excretion. Notwithstanding the slight gain of weight in milder cases, he concluded that tuberculosis runs its regular course uninfluenced by insulin therapy. Insulin should be used only in mild, stationary or very slightly progressive cases. In severe or active cases, insulin was held responsible for increased fever, haemoptysis, spontaneous pneumothorax and some actually fatal results, and was therefore contraindicated.

Ager reported a case with increase of blood-sugar under insulin treatment. He shared the current view that insulin should not be used in acute or febrile tuberculosis, but that it may sometimes be of aid against malnutrition.

Arnold described treatment for as long as 6 weeks in two series of respectively 20 and 15 cases of tuberculosis, with insulin as high as 15 to 25 units, t. i. d. In 23 cases there were gains of 2 to 12 lbs. of weight. No bad effects were seen. On the contrary, the greatest benefit was in a woman with far-advanced disease in both lungs, cough, expectoration, and fever up to 102°, who with insulin became able to eat well, to leave her bed, and be up and about the hospital with temperature down to 99–100°.

Barker, lecturing on a tuberculosis patient aged 20 years, with pleurisy and temperature up to 104.5°, reviewed the current warnings concerning care and possible danger in the use of insulin, but expressed himself in favor of the treatment with doses not above 30 units per day. He suggested the plan of three courses of 2 weeks interrupted by intervals of 2 weeks. The benefits were increased appetite, weight and strength, often continuing after the stopping of insulin.

Leggett and Callahan in 1931 reported very valuable observations on a series of 13 cases extending back to 1929. One rational feature was that they did not give "courses" of insulin, but continued until there was either definite improvement or a fair trial of the method. Their dosage was low, usually 3 to 5 units, sometimes 7 to 10 units, t. i. d., and the duration varied from a few days or weeks up to 3 or 6 months. Among

the 13 cases 8 were far advanced; but 12 gained from 1½ to 18 lbs. and one was stationary. A patient with advanced pulmonary tuberculosis, enteritis and possibly peritonitis gained 1½ lbs. in 8 weeks. For comparison, a patient with inoperable carcinoma and lung metastases, who had lost 80 lbs., made no lasting gain with insulin. Insulin was also tried by special request in 7 hopelessly ill patients, too weak to be weighed. There was temporary improvement of appetite in 5, but no lasting benefit. In the entire experience there were never any bad effects of insulin as respects fever, lung lesions, menstruation, or other focal or general reactions, except for one case of urticaria. The authors favored insulin particularly for overcoming the anorexia, emaciation and weakness which are serious features of many cases of tuberculosis.

Ellman published one case of illustrating marked benefit from insulin, but at the same time he shared the traditional view that cases must be carefully selected, that the dosage should not exceed 30 units per day or be continued beyond 2 or 3 weeks, and that among the contraindications are fever, active infection, haemoptysis, marked hypotension, and severe reaction following the injection.

Heaton proceeded along somewhat the same lines as Leggett and Callahan. His insulin doses were from 5 to 15 units, t. i. d., adjusted to suit individual needs, and continued sometimes for 3 or 4 months. In 5 "acutely active or terminal cases" there was no real benefit, though in one there was a gain of 1¾ lbs., and in another a steady loss of weight was checked for three weeks. Among "febrile cases of low grade activity," 7 were distinctly and 3 strikingly benefited. "No. 11 suffered local allergic reactions which apparently led to hemoptysis." Of 5 afebrile patients, 2 were benefited, 1 had an inadequate trial, and 2 stopped insulin because the reactions were unpleasant. To the objection that beneficial gains of weight must be merely a sequel to the healing of the tuberculosis, the author replied that deficiency of appetite and weight is in itself a definite handicap to recovery in many cases. He also suggested that allergic troubles might be avoided, when necessary, by the use of crystalline insulin.

Banyai and Jurgens (1934) summarized their observations of 43 cases of pulmonary tuberculosis as follows. "Insulin therapy was found to be of value in that it improved the appetite in 19 (79.1 per cent) of the 24 moderately advanced cases and in 11 (57.8 per cent) of the 19 far-advanced cases. It increased the weight in 13 (54.1 per cent) of the moderately advanced and in 9 (47.3 per cent) of the far-advanced cases."

Rosenberg and Kereszturi have described an acceleration of the rate of gain in weight in 15 out of 17 tuberculous children with the use of insulin. Of these, 13 maintained the gain during follow-up periods of 3 months after the discontinuance of insulin.

REVIEW

The following interpretation may be made of the existing state of the literature at the time this work was begun and also when our preliminary papers were published.

1. Although the number of authors reporting benefit was greater than the number who reported harm, the preponderant evidence was adverse to insulin in nondiabetic tuberculosis cases. The pioneer work in this field stimulated an outburst of interest and investigation, especially between 1927 and 1930, which died away without practical result. The opponents remained opposed, whereas the advocates who wrote enthusiastically of the immediate results seem quietly to have abandoned the method for regular use in tuberculosis; or, if there ever has been such adoption anywhere, no reports of the prolonged experience have been published, and there has been no general use of insulin among tuberculosis specialists or tuberculosis patients.

2. The peculiar mixture of good and bad reports invites closer analysis. The striking nutritive benefits witnessed by so many reliable observers should scarcely be ignored with reference to a disease in which nutrition is such an important factor as in tuberculosis. On the other hand, the failures and mishaps described by other writers may be largely explainable. Turning to the complication of diabetes with tuberculosis, we find in the paper of Weskott equally grave examples and warnings of the dangers of insulin, and yet abundant subsequent experience has proved that these difficulties are seldom serious and that the treatment of tuberculous diabetics with insulin, even in very large doses, is on the whole a brilliant success. In addition to the exaggerated dread of hypoglycaemia and the general inexperience and timidity of some of the early writers on insulin, causing them to blame it for anything that might go wrong during treatment, attention may be directed to Dünner and Dohrn's analyses of 6 brands of German and other insulin in 1928, showing in 100-unit samples variations of protein content from 2.73 to 9.88 mgm., and of total dry solids from 0.0053 to 0.3 gm. Other writers also have attributed a large share of the reported allergic injuries to impure insulin. Therefore the quality of insulin now available commercially may open up new therapeutic possibilities.

3. The blind following of a plan originated by Falta, together with fears of allergic reactions, resulted in a fantastic form of clinical trial of insulin, namely, the custom of giving it for about 3 weeks and observing whether the patients gained weight within this time and whether this weight was retained for some weeks or months afterward. One might imagine a similar pronunciamento on bed-rest by writers who would say, "We put our patients to bed for 3 weeks; there were temporary improvements in temperature, weight and various symptoms; but these benefits were lost when the patients got up, and therefore confinement to bed is worthless." Likewise no such basis of judgment would ever be accepted for codliver oil or other vitamine preparations, or for any other medical measure. Because of this erroneous foundation, the great mass of the literature on insulin in tuberculosis can be discarded. The few writers who have tried longer treatments have had, on the whole, encouraging results. Especially the scanty literature since 1930 was reviewed separately in order to show that, along with writers following the old errors, there are several who have undertaken rational application of insulin with sufficient success to warrant adoption of it as a practical rather than an experimental method. Reference may be made to the use of insulin in individualized dosage mentioned above, and to the suggestions in our preliminary papers (2) (3) that insulin is an anabolic hormone, which may conceivably have an influence beyond the mere gain of weight in improving general vigor and resistance and modifying the soil upon which the tuberculous infection develops. For these reasons insulin seems at least worthy of a trial on the same basis as any other therapeutic measure in tuberculosis, namely by gradually acquiring skill in applying it to the best advantage for the needs of the individual patient, in dosage and over a duration of time to be determined by observation.

Several papers contemporaneous with or subsequent to our work have arrived at the same conclusions, and the insulin treatment seems now to be established as a part of the practical management of a rather large class of tuberculosis cases.

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INSULIN IN THE TREATMENT OF TUBERCULOSIS

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This paper is in sequence with earlier preliminary publications (1) (2) (3) and with the preceding bibliographical paper (4).

The observations were made upon patients in the Valley View Sanatorium (Paterson, New Jersey), who had been under its institutional regimen for a long enough time for complete study and judgment of their condition, mostly for a considerable number of months before the beginning of insulin treatment. The tables have been made full enough to explain most details. The blood-sugar analyses were done by the Benedict method, and the sedimentation tests by the Cutler method.

After completion of their insulin treatment, most of the patients have remained under observation until death or until the present time.

Tests of carbohydrate assimilation were made in a series of 128 patients, representing a rough cross-section of tuberculosis in its various aspects, ranging from the almost healed ambulatory down to the hopeless dying states. None of these patients were on insulin therapy prior to or at the time of the tests, although subsequently a number of them received the treatment. From the total number we were able to secure 117 complete tests. The tests included a blood-sugar one hour after the ordinary supper, one fasting, and three one-hourly after the ingestion of 100 gm. glucose (morning, without breakfast), making a total of five blood-sugar determinations. There were 11 incomplete tests occasioned by the inability of the patients to retain the glucose. However, of these, we secured at least the after-supper and fasting figures. The total series necessitated the collecting and examination of over 600 single samples of blood.

Each patient was classified as to age, sex, weight, duration of disease, temperature, pulse-rate, sputum, bacteriology, pathological classification, surgical procedures and blood-sedimentation time. To this the corresponding blood-sugar determinations were annexed for a comparative study.

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TABLE 1

Glucose tolerance in tuberculosis

NAME	AGE	PULSE	TEMPERATURE	WEIGHT	SPUTUM	DURATION	CLASSIFICATION	COMPLICATIONS	SURGICAL PROCEDURES	BLOOD SEDIMENTATION	P.M.	A.M.	1ST HOUR	2ND HOUR	3RD HOUR
M. G.	31	80–96	97–99	−30	Neg.	11 years	M.A.A.	None	None	None	107	97	184	150	88
W. D.	24	90–100	97.6–98	−26	Neg.	1–5 months	M.A.A.	None	Phrenic; attempted pneumothorax	26/ hour	115	97	108	126	94
M. P.	23	80–100	98–98.6	−15	Neg.	3 years	M.A.A.	None	None	24/ hour	130	101	169	126	122
T. B.	27	66–96	98–99	−17	Neg.	6 years	Observ.	None	None	None	107	92	125	119	106
M. S.	48	70–90	98–99	−32	Pos.	10 years	F.A.A.	None	None	None	115	104	189	136	99
F. G.	20	60–86	97.6–98.6	−6	Pos.	2–3 months	F.A.A.	None	Unsuccessful pneumothorax	4.2/ hour	107	102	126	129	94
A. A.	30	76–96	97.4–98.6	+1½	Pos.	10 years	F.A.A.	Effusion	Phrenic; pneumothorax	10/ hour	104	111	180	136	143
F. G.	17	60–86	97–99	−36	Neg.	1 year	F.A.A.	None	None	26/ hour	105	102	187	126	121
J. H.	28	80–90	97–98.6	−16	Pos.	5 years	F.A.A.	Tuberculous enteritis	None	16/ hour	122	98	133	83	61
J. L.	33	86–90	97.6–98	−28	Pos.	3 years	F.A.A.	None	Unsuccessful pneumothorax; phrenic	28/ hour	131	92	234	180	119
J. G.	35	80–100	98–99	+20	Neg.	2 years	M.A.A.	None	None	5.5/ hour	107	98	206	109	120
D. C.	48	86–110	97–99	−55	Pos.	4½ years	F.A.A.	None	None	26/ hour	139	105	206	150	132
E. B.	50	90–116	97.6–99	Normal	Pos.	12 years	F.A.A.	Prostatic hypertrophy; gastric ulcer (?)	Unsuccessful pneumothorax	5.5/ hour	120	98	157	127	70
A. S.	60	90–120	97–98.6	−26	Neg.	4 months	M.A.A.	None	None	4 mm.	137	117	263	122	71
L. P.	21	86–110	98–99.6	+4	Pos.	1 year	F.A.A.	None	None	Not done	142	93	183	101	75
M. M.	14	90–120	97–99	Normal	Neg.	5 months	M.A.A.	None	Pneumothorax	Not done	106	97	132	121	97
T. W.	48	80–110	97.6–100	−15	Pos.	9 months	F.A.B.	Syphilis	None	Not done	127	98	180	168	127
J. G.	41	86–100	98–99	+2	Pos.	2 years	F.A.A.	None	None	24/ hour	107	78	103	114	106
K. v. H.	18	86–110	98–98.6	−10	None raised	2 years	F.A.A.	Effusion	Pneumothorax	13/ hour	77	75	108	80	80
M. L.	57	80–100	97–98.6	−42	Neg.	11 months	M.A.A.	None	None	23/ hour	117	107	209	166	138
R. T.	26	80–96	97.6–99	+14	Pos.	1 year	M.A.A.	None	None	6/ hour	148	117	207	154	117
E. M.	28	80–86	98–99	+3	Neg.	9 months	Min. A.	None	None	4/ hour	106	104	132	120	102
L. F.	62	86–96	97–99	−18	Pos.	2–10 months	F.A.A.	None	None	18/ hour	137	111	127	120	91
G. I.	36	86–100	97–99	Normal	Neg.	3½ years	F.A.A.	Chronic sinusitis	Pneumothorax	15/ hour	143	115	145	111	61
M. v. T.	41	80–100	98–99	Normal	Pos.	6 years	F.A.A.	None	Unsuccessful pneumothorax	22/ hour	180	127	272	171	104
S. Z.	30	80–96	98–98.6	+18	Neg.	1½ years	M.A.A.	None	Unsuccessful pneumothorax; phrenic	3.2/ hour	107	111	154	133	114
J. McK.	15	86–106	98–99	+26	Neg.	1½ years	Min. A.	Pleural effusion	None	2.5/ hour	105	98	143	120	92
W. G.	20	80–96	97–99	−17	Neg.	3 months	Min. A.	None	None	12/ hour	113	100	90	111	120
S. G.	42	90–96	98–98.6	−12	Neg.	1–2 months	M.A.A.	Osteoarthritic spine	None	20/ hour	123	107	150	126	121

J. D.	34	86–96	98–98.6	+32	Pos.	9 months	M.A.A.	Tuberculous laryngitis	Pneumothorax; phrenic	4/ hour	120	105	206	159	169
M. R.	42	86–106	98–99	−30	Neg.	9 years	M.A.A.	None	None	5/ hour	138	112	156	128	113
R. H.	27	80–100	98–98.6	−21	Neg.	1½ years	M.A.A.	None	Pneumothorax	12/ hour	136	126	256	200	116
L. H.	47	82–104	98–98.6	+13	Pos.	1–3 months	F.A.A.	Tuberculous epididymitis	Unilateral orchidectomy	8.5/ hour	138	98	182	189	127
H. S.	22	70–90	97–98.6	−17	Neg.	14 months	F.A.A.	None	Pneumothorax	4 mm.	107	104	138	131	128
O. M.	58	80–116	97.6–99	−32	Pos.	13 months	M.A.A.	None	None	24/ hour	139	122	223	162	130
C. C.	63	80–100	97–99	−8	Pos.	1–6 months	F.A.A.	Tuberculous enteritis	None	26/ hour	109	108	162	166	105
E. Z.	52	76–84	97.4–98.6	−16	Pos.	1 year	F.A.A.	None	Pneumothorax	6.5/ hour	109	114	133	127	104
C. B.	34	76–86	97.6–98.6	+26	Neg.	2–3 months	F.A.A.	Syphilis	Pneumothorax	None	122	109	118	103	79
A. F.	33	80–100	97.6–98.6	+30	Pos.	12 years	M.A.A.	None	Pneumothorax	14.5/ hour	123	114	217	126	106
A. L.	26	80–96	99–100	−12	Neg.	2–4 months	F.A.B.	Pleural effusion; chronic rheumatic heart	Pneumothorax	None	136	108	131	105	90
C. S.	15	100–124	98–101	−27	Pos.	6 months	F.A.C.	Tuberculous laryngitis; tuberculous enteritis (?)	Phrenic	Very rapid	150	100	238	184	114
R. S.	17	90–110	99–103	−10	Pos.	7 months	F.A.C.	Pleural effusion	Pneumothorax; phrenic	28.5 mm.	145	99	119	99	88
E. M.	28	80–106	98–99	−25	Pos.	2 years	F.A.A.	Pleural effusion	Pneumothorax	None	136	95	106	96	108
L. v. L.	40	74–86	97.6–100.2	∓58	Neg.	1 year	F.A.B.	Pleural effusion; syphilis	Pneumothorax	None	142	99	242	162	122
R. C.	21	80–106	99–102.6	−16	Pos.	14 months	F.A.C.	Maxillary sinusitis	Phrenic; pneumothorax	None	115	88	178	120	106
H. F.	24	90–108	99–100	−8	Pos.	5½ years	F.A.B.	Tuberculous enteritis	Pneumothorax; phrenic	None	104	93	162	133	104
L. R.	20	80–106	98–100	−6	Pos.	3 years	F.A.B.	Pleural effusion	Pneumothorax; phrenic	None	118	98	238	226	168
T. E.	24	80–106	97.6–98.6	−28	Neg.	1 year	F.A.A.	Tuberculous empyema	Pneumothorax	None	111	99	175	115	112
D. D.	44	80–100	98–101.2	+5	Pos.	2 years	F.A.C.	None	Pneumothorax	21 mm.	152	118	169	154	148
C. W.	37	80–106	97.6–99.6	−18	Pos.	1–4 months	F.A.A.	Pulmonary abscess	None	29 mm.	173	108	203	124	108
M. R.	43	70–90	97–98.6	−4	Pos.	4 months	F.A.A.	None	None	25 mm.	133	93	130	84	78
W. J.	26	80–100	97–98.8	+15	Pos.	1 year	F.A.A.	None	Thoracoplasty	None	120	102	146	150	115
L. S.	36	90–100	98–100.6	Not weighed	Pos.	5 years	F.A.B.	None	None	26 mm.	173	100	180	223	166
W. L.	18	80–100	99–100.6	−25	Pos.	3 months	M.A.B.	None	Pneumothorax	27 mm.	159	111	217	170	129
W. J.	39	80–100	98–100	−25	Pos.	7 months	M.A.B.	Pleural effusion; syphilis	Pneumothorax	27 mm.	129	112	173	166	124
A. G.	39−	90–110	98–100	−21	Pos.	10 years	F.A.B.	None	Pneumothorax, discontinued; phrenic	None	150	107	214	206	103
L. F.	16	80–126	97–100	+2	Pos.	1 year	F.A.B.	None	None	None	115	88	148	93	81
D. C.	23	80–106	99–100.6	−20	Pos.	5 years	F.A.B.	None	Pneumothorax, discontinued	None	145	104	140	162	123
J. S.	45	80–100	98–99.6	+24	Pos.	2 years	F.A.A.	Pleural effusion; syphilis	Pneumothorax, discontinued	25 mm.	182	130	254	180	91
J. R.	47	80–100	98–99.6	Bed	Pos.	20 years	F.A.A.	Pleural effusion	Pneumothorax; phrenic	25 mm.	142	112	180	195	137
J. S.	42	80–96	96.6–99	−33	Pos.	8 months	F.A.A.	None	None	Not done	120	97	157	131	101
H. S.	45	96–126	97–100.2	−46	Pos.	7 months	F.A.B.	None	None	Not done	112	98	139	127	103
F. B.	23	80–100	97–99.6	−33	Pos.	6 weeks	F.A.A.	None	None	25/ 1 hour	116	88	136	89	94

Min. = minimal; M.A. = moderately advanced; F.A. = far advanced; A = slight; B = moderate; C = severe.

TABLE 1—*Concluded*

NAME	AGE	PULSE	TEMPERATURE	WEIGHT	SPUTUM	DURATION	CLASSIFICATION	COMPLICATIONS	SURGICAL PROCEDURES	BLOOD SEDIMENTATION	P.M.	A.M.	1ST HOUR	2ND HOUR	3RD HOUR
S. F.	28	86–120	98–100.6	+11	Pos.	18 months	F.A.B.	None	None	20.5 mm.	117	100	136	101	78
C. F.	20	86–120	98–102	−44	Pos.	10 months	F.A.C.	Tuberculous laryngitis	None	Not done	116	93	121	136	115
H. G.	36	86–96	98–99.6	Normal	Pos.	7 years	F.A.A.	Syphilis	Pneumothorax, discontinued	Not done	140	112	171	128	120
M. C.	19	70–90–	97–98.6	+6	Neg.	3 months	Min. A.	None	None		111	107	150	105	86
A. H.	21	76–90	97–99	−6	Pos.	4 years	F.A.A.	None	Pneumothorax, discontinued; phrenicotomy	Not done	112	96	195	130	110
E. V.	39	70–100	98–99.6	−8	Pos.	5 years	F.A.A.	None	Phrenic; pneumothorax discontinued	Not done	120	111	187	115	76
H. S.	20	70–90	98–99	−5	Pos.	22 months	M.A.A.	None	Pneumothorax	Not done	88	80	107	91	78
T. D.	55	80–96	97–99.2	−45	0	5 years	F.A.A.	Chronic tuberculous laryngitis	None		130	120	230	187	156
B. A.	23	80–100.6	97–99.6	−12	Pos.	3 months	M.A.A.	None	None	27 mm.	93	76	136	115	98
W. G.	27	80–110	96.8–99.2	In bed	Neg.	4 months	F.A.A.	Syphilis	Pneumothorax, discontinued	Not done	129	108	150	136	115
J. B.	47	76–100	96.2–99	−17	Neg.	3 years, 1 month	F.A.A.	Dementia praecox	Pneumothorax	Not done	125	100	166	125	108
C. S.	31	70–88	96.6–98.6	Not weighed	Neg.	27 months	F.A.A.	Tuberculous hip-knee-spine	Aspiration abscesses	Not done	112	107	110	88	78
J. S.	15	80–112	98–101	—	Neg.	20 months	M.A.A.	Tuberculous hip and knee	None	Not done	223	88	180	234	115
J. v. der P.	40	76–90	98–99.2	−17	Pos.	7½ years	F.A.A.	None	Phrenicectomy	25 mm.	159	104	142	171	189
J. di P.	33	80–93	97.6–99.2	Too ill	Pos.	2½ years	F.A.A.	Tuberculous shoulder and elbow	Incision abscess		166	87	220	175	153
I. L.	14	80–90	97.6–99	−4	Pos.	5 months	M.A.A.	None	Phrenic; attempted pneumothorax		118	105	272	199	117
J. H.	39	70–86	97–98	−30	Pos.	9 years	M.A.A.	None	Attempted pneumothorax; phrenicectomy	16.8 mm.	156	133	300	326	220
M. B.	48	90–100	97–99	−26	Pos.	1½ years	F.A.A.	Pleurisy with effusion; tuberculous enteritis	Pneumothorax; phrenicectomy	0	130	111	189	270	226
A. B.	38	96–116	98.6–100.8	Too ill	Pos.	5 months	F.A.B.	None	None	0	160	150	170	200	184
G. R.	29	76–92	98.6–99.2	+16	Pos.	1 month	M.A.A.	None	None	25/hour	145	105	226	187	112
C. de C.	33	80–100	97.6–99	−13	Neg.	4 months	M.A.A.	None	Pneumothorax	28/hour	187	112	156	129	125
W. W.	77	80–98	97–99.4	−24	Pos.	17 years	F.A.A.	None	None	33.5/hour	171	110	249	164	137
E. R.	52	80–90	97.6–99.2	−14	Pos.	5 years	F.A.A.	Tuberculous epididymitis	Epididymectomy-vasectomy with resection	26 mm./hour	150	146	166	206	125
A. H.	47	90–106	97.6–99.6	−2	Pos.	20 years	F.A.A.	Pleural effusion	Pneumothorax; phrenic	14.5/hour	175	121	187	162	142
I. L.	22	80–98–	97–99	+10	Pos.	10 months	F.A.A.	None	Pneumothorax	18/1 hour	155	106	166	132	79
H. T.	22	80–96	98.6–99	−31	None	3 years	F.A.A.	Traumatic anaesthesia; traumatic osteomyelitis of left small toe	Pneumothorax; phrenic	24 mm.	126	112	184	105	116

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D. K.	43	66–80	97–98.6	−6	Pos.	1½ years	F.A.A.	None	None	23/ 1 hour	138	97	157	150	120
J. P.	30	66–76	97.8–99	−30	Pos.	4 months	F.A.A.	None	Pneumothorax	24.5 mm.	129	100	168	121	92
J. V.	44	60–80	97.6–98.6	−33	Neg.	6 months	F.A.A.	None	None	4 mm.	119	101	150	107	55
F. C.	22	90–100	98–99.6	−40	Pos.	6 years	F.A.A.	None	Phrenic	2 mm./ hour	166	108	169	206	168
I. C.	25	80–96	97.6–99	−19	Pos.	13 months	F.A.A.	Pleural effusion	Pneumothorax	15.2 mm./ 1 hour	150	131	192	195	138
E. M.	37	80–98	98–99.6	−15	Pos.	5 years	F.A.A.	None	Pneumothorax; phrenic	25 mm./ 1 hour	180	107	230	140	133
J. L.	51	82–99	97–99.6	−59	Pos.	8 years	F.A.A.	Renal tuberculosis and tuberculous cystitis	None	Not done	131	97	173	136	116
S. M.	26	70–90	99–100.6	−3	Pos.	1 year	F.A.B.	None	Attempted pneumothorax; phrenicectomy	Not done	150	134	195	153	120
R. W.	60	76–86	97.6–98.6	+7	Pos.	1 year	F.A.A.	None	Pneumothorax	23/ 1 hour	199	121	220	263	230
J. G.	29	80–90	97–98.6	−8	Pos.	8 years	F.A.A.	None	Pneumothorax	10/ 1 hour	115	111	189	203	116
A. S.	22	86–96	97.6–98.6	−28	Pos.	2 years, 2 months	F.A.A.	None	None	26.5/ hour	117	105	199	192	145
C. W.	51	80–96	97.6–99	−19	Pos.	8 months	F.A.A.	None	None		107	90	180	171	150
A. T.	26	90–96	98–98.6	−28	Pos.	14 months	F.A.A.	Chronic sinusitis; chronic tonsillitis	Pneumothorax	20 mm./ 1 hour	131	117	184	146	131
M. C.	29	70–86	98–99.6	+6	Neg.	5 years	M.A.A.	Healed tuberculous laryngitis	Pneumothorax; phrenic	10 mm./ 1 hour	154	95	159	137	104
L. J.	23	100–120	97.6–98.6	−31	Pos.	3 years	M.A.A.	None	Pneumothorax	18 mm./ 1 hour	87	102	160	93	111
M. B.	33	70–96	97–99	+9	Pos.	2 years	M.A.A.	Rectal fistula	Pneumothorax	27/ 1 hour	140	106	217	159	154
V. U.	27	76–96	97.6–99	Normal	Pos.	4 years	M.A.A.	Chronic tonsillitis; chronic otitis media	None	20.5/ 1 hour	108	102	192	123	96
F. R.	41	80–84	97.6–99	−16	Neg.	9 months	Min. A.	None	None	15/ 1 hour	117	101	166	98	106
A. W.	17	80–96	98–99.6	−3	Pos.	17 months	M.A.A.	Pleural effusion (small)	Pneumothorax	Not done	166	104	182	143	102
S. S.	40	74–92	98–99.2	−5	Neg.	3 years	F.A.A.	Tuberculous bladder and kidney	Nephrectomy, right kidney	Not done	129	99	178	138	110
R. L.	14	100–136	97–99.2	−20	Pos.	3 years	F.A.A.	None	Pneumothorax	Rapid	162	123	288	288	263
R. W.	24	80–112	98.6–100.6	−22	Neg.	1 year	M.A.B.	Syphilis	None	24.5/ hour	103	91	154	122	87
N. R.	32	80–90	97–99	−30	Neg.	4 years	F.A.A.	None	Pneumothorax	19/ hour	126	84	230	145	120
A. C.	38	80–100	98–99	Bed	Neg.	4 years	Nontuberculosis	None	None	Not done	127	105	182	123	114
E. W.	23	80–100	98–100.6	−6	Pos.	6 years	F.A.B.	None	Bilateral pneumothorax	None	112	93	162	146	130
E. S.	41	90–120	97.6–99.6	−42	Pos.	8 years	F.A.A.	Laryngeal and gastrointestinal tuberculosis	None	None	160	135	238	182	157
M. C.	42	86–120	97–98.6	−30	Pos.	14 months	F.A.A.	Pleural effusion	Phrenic; attempted pneumothorax	23/ hour	157	106	211	192	137
B. W.	31	82–120	97–99	−18	Pos.	2½ years	M.A.A.	None	None	22/ ½ hour	132	104	164	137	115
F. M.	49	80–100	97–99	−24	Pos.	4 months	F.A.A.	None	None	21/ hour	150	93	110	116	84
E. G.	17	80–100	98–99.4	+7	Pos.	10 months	F.A.A.	None	Pneumothorax	5/ hour	98	150	150	110	103

The findings confirmed the reports of previous authors that there is frequently a demonstrable reduction of sugar-tolerance in tuberculous patients. Of the entire group of 128, only three exhibited an abnormally high blood-sugar one hour after the ordinary supper, and only one revealed a slightly elevated fasting figure. Nevertheless, after the ingestion of 100 gm. glucose on a fasting stomach, 47 of the 117 patients, or approximately 40 per cent, presented elevated tolerance curves of one type or another. This unquestionably pointed to a comparative tolerance-loss which could only have been detected or elicited by large quantities of carbohydrate in a readily assimilable form such as glucose. An attempt was made to associate these responses or lack of responses with any one or more of the clinical or laboratory data. Also, further investigation was directed to a possible relationship between the character of the curve and the patient's ability to react to treatment with insulin. the thought being that perhaps those patients embarrassed by a loss of tolerance might be proportionately more responsive than those presenting normal or subnormal curves.

The general conclusions regarding all aspects were of a negative character. The nature of the tolerance curve could not be linked with any of the accumulated data, nor was there any direct relationship whatever between the curve and the nature of the patient's response to insulin therapy. The most severe cases exhibited high as well as low curves, and the same thing was true of the milder infections. Since the completion of our data there have been 10 deaths within the group. Later examinations of their carbohydrate tolerance revealed no regularity, for exactly one-half presented normal curves and the other half elevated readings. Of the afore-mentioned group, six were later included among those taking insulin.

In 4 cases the glucose tolerance tests were repeated after a period of insulin treatment, as shown in table 2.

TABLE 2

NAME	FIRST TEST					INTERVAL BETWEEN TESTS	REPEAT				
	P.M.	A.M.	1	2	3		P.M.	A.M.	1	2	3
						weeks					
I. C.*	142	102	192	195	136	9	91	108	223	173	129
N. R.*	126	84	230	145	120	6	175	119	300	246	171
W. D.†	103	91	200	195	80	6	115	97	108	126	94
M. P.*	125	115	178	142	107	8	130	101	169	126	122

* Insulin dose, 10 units, t.i.d.

† Daily insulin, 15–10–15 units.

On the whole these results (table 2) display no important tendency to lowering of the tolerance with the insulin treatment, though it is recognized that a purely temporary lowering can actually occur in some cases, especially with higher insulin dosage.

Table 3 summarizes the records of 27 cases which were treated with insulin long enough to form a judgment of the results. As will be evident from the classification and description, most of these were severe or actually hopeless in character. A cure therefore was not anticipated in such cases, and the question was only whether insulin might accomplish any temporary alleviation of the condition or prolongation of life. Statistical discussion of the mortality is therefore omitted as foreign to the purpose. The insulin administration was usually begun at 5 units, one to three times per day, and increased more or less rapidly according to the tolerance of the patient to the dosage shown in the table. The patients were given lunches, as liberal as possible in both carbohydrate and fat, between meals and at bedtime. With these six regular feedings per day there was seldom any difficulty with insulin reactions, but, if such were encountered, they were treated with the ordinary carbohydrate administration. No harmful results were observed from the reactions or from the insulin in general. Allergic manifestations were rare. A few patients were uncoöperative, but the majority became enthusiastic over the gains in weight and strength and were eager to have the treatment begun and continued. The greatest benefits were naturally observed with asthenic cases and in preoperative or postoperative care. Naturally, also, the least effect was obtained in the severest cases with fever and intoxication.

SUMMARY AND CONCLUSIONS

A. Concerning Carbohydrate Assimilation

1. Among 128 patients representing all types and degrees of tuberculosis, approximately 40 per cent showed abnormally high blood-sugar curves after administration of 100 gm. glucose, while alimentary hyperglycaemia after ordinary meals was found in only 3 persons, and a slight fasting hyperglycaemia in only one individual.

TAB
Therapeutic re

NAME	SEX	AGE	CLASS	OPERATIONS AND COMPLICATIONS	SYMPTOMS	DURATION OF TREATMENT. MAXIMUM INSULIN DOSAGE
C. M.	F.	25	F.A.A.	Pneumothorax, 3/4/30; phrenic neurectomy, 8/18/31	During 15 months patient's weight fluctuated. Languid. Had anorexia, occasional vomiting, flatulence, indigestion. Irritable and nervous. Bed-patient 6 months prior to insulin therapy. Sputum positive. X-ray: caseous left.	7/ 8/32 to 2/ 3/33 U, xx, tid.
N. R.	M.	32	F.A.A.	Artificial pneumothorax, 1/4/32: pleural effusion, 7/7/32	Condition stationary during 15 months. Following effusion had loss of weight, anorexia, increased cough, and expectoration. X-ray: lesions stationary. Sputum negative.	8/ 3/32 to 10/28/32 U, x, tid.
J. R.	M.	48	M.A.B.	Pneumothorax, 12/17/31; phrenic neurectomy, 4/18/32; pleural effusion, 4/7/32; thoracenteses: 10/22/32; 12/31/32	15 years' duration. Frequent attacks of sinusitis, profuse expectoration, 4 oz. daily; extreme nervousness; frequent headaches. Fever 100°. General condition stationary; sputum positive. X-ray: fibrocaseous right. Exudative left.	7/24/32 to 11/20/32 U, xx, tid.
A. C.	F.	25	F.A.A.	Attempted artificial pneumothorax, 2/8/32; phrenicectomy, 2/22/32; thoracoplasty: 1st, 2/22/33; 2nd, 3/6/34	Curing for 4 years; had made no progress; lassitude, loss of strength; persistent hacking cough. Hoarseness from laryngitis. X-ray: cavity left. Sputum continued positive.	7/ 7/32 to 9/23/32 U, xx, A.M.; U, xv, M and P.M.
F. C.	M.	21	F.A.A.	Phrenic neurectomy, 10/27/31; artificial pneumothorax, 1/22/34	During residence had gained 16 lbs. Had no symptoms. Ambulant 3/5/32. Fever 4/28/32 to 7/13/32; lost 20 lbs.; fever 101°. Nausea; severe anorexia. Cough and expectoration increased. Sputum positive. X-ray: no change in multilocular cavitation; marked increase in infiltration, bilateral. Tuberculous bronchopneumonia, left upper lobe.	7/19/32 to 4/13/33 U, xx, tid., until 2/8/33 U, v, tid. 2/8/3 to 4/13/33

LE 3
sults with insulin

WEIGHT IN POUNDS				RED BLOOD CELLS			HAEMOGLOBIN			SEDIMENTATION			RESULTS
Standard	Before	After	Present	Before Insulin	After Insulin	Present	Before Insulin	After Insulin	Present	Before	After	Present	
Insulin													
124	98	134	95	3,360	3,760	2,800	70	78	50	20	16	13	Strength increased rapidly, after three weeks gastric symptoms disappeared. After 2 months, cough disappeared, expectoration decreased 50 per cent. Was made ambulant; had relapse of all symptoms. Cavity increased in size. Three-stage thoracoplasty completed 3/11/33. Sputum positive. Lost 12 lbs. before operation.
136	106	103½	109½	3,720	3,340	3,880	75	72	75	19	25	16	Patient always complained of anorexia, languor. After pneumothorax had chilliness, fever, nervousness. When had Ux began to have reactions frequently: symptoms, nervousness, increased hunger, perspiration. X-ray: lesion same. After insulin was discontinued, began to feel stronger. Appetite improved; weight from 100 to 111 lbs. Present: sputum negative; X-ray, no change.
176	130	163	—	3,380	4,400	—	77	90	—	25	26	—	Appetite increased; sinus discharge decreased (50 per cent). Headaches and nervousness disappeared. Mild reaction, 11/20/32 (nervousness, tremor and extreme hunger). Sputum remained positive and X-ray cavity open. Increased fibrosis, right side. Selective thoracoplasty recommended. Gained 10 lbs. after insulin was discontinued. Patient discharged 5/26/33; very ill at present.
127	118	134	124, etc.	3,760	3,800	3,920	74	73	78	22	22.5	28	Increase in appetite and strength. Temperature became normal; cough and expectoration decreased; became ambulant. Cavity remained open, but remainder of lung improved; sputum positive. Reactivity of laryngitis, April, 1933. Increased infiltration, right upper lobe, after laryngitis became active. Convalescing from second-stage thoracoplasty. Sputum negative. Condition most favorable since admission.
134	100	136	151	3,620	4,200	4,000	68	84	85	24.5	19	13	Appetite improved; nausea decreased; vomiting ceased; hunger returned. Temperature normal in six weeks; expectoration decreased from 4 oz. to one; gained 36 lbs. until 2/8/33. Insulin decreased to Uv, tid, until 4/13/33, when discontinued. Weight remained stationary during that interval. Continued to gain weight after insulin was discontinued; sputum remained positive. X-ray: bronchopneumonia resolved; increased fibrosis, and left upper lobe; decreased infiltration, right. Present: continued improvement in X-ray; tolerates increased exercise. Prognosis most favorable since admission.

TABLE 3—

NAME	SEX	AGE	CLASS	OPERATIONS AND COMPLICATIONS	SYMPTOMS	DURATION OF TREATMENT. MAXIMUM INSULIN DOSAGE
H. G.	M.	25	F.A.A.	Unsuccessful attempt to reëstablish artificial pneumothorax, 12/8/32; phrenicectomy, 12/27/32	Long sanatorium regimen prior to admission here; loss of weight 30 lbs. Anorexia, nausea, indigestion, loss of strength, bilateral cavitation. Sputum positive. 1/14/33: had acute pain in epigastrium. Refused to cooperate further.	12/ 8/32 to 2/18/33 U, xx, tid.
E. K.	F.	28	F.A.A.	Phrenicectomy, 6/1/32	Usual symptoms of tuberculosis; underweight, 36 lbs. X-ray: cavitation, 2nd i.s. left; exudative right. Sputum negative.	6/ 2/32 to 7/13/32 U, xx, tid.
G. P.	F.	24	Min.	None: chronic tonsillitis	Cough, expectoration; acute attacks of tonsillitis and pharyngitis, with fever and anorexia. X-ray: exudative lesion to 3rd rib. Sputum negative.	7/30/32 to 10/ 5/32 U, x, tid.
M. W.	F.	26	F.A.C.	Artificial pneumothorax, 11/24/30; pleural effusion, 12/15/30; phrenic neurectomy, 5/20/32	All symptoms decreased for 1 year. After one year relapsed; fever 100°, lost 19 lbs. Developed indigestion, epigastric pain, anorexia, nausea, progressive loss of weight. X-ray: bilateral caseous pneumonia. Sputum positive.	9/24/32 to 11/15/32 U, x, tid.
I. C.	M.	25	F.A.A.	Artificial pneumothorax, 8/28/31; attempted bilateral artificial pneumothorax, 3/25/31; pleural effusion, 7/24/32	Patient had made no appreciable progress during 1 year of residence. Fever 99°. Cough and expectoration. Indigestion. X-ray: cavity, left upper lobe; infiltration, right upper. Sputum positive.	7/20/32 to 2/ 8/33 U, xx, tid.

Continued

WEIGHT IN POUNDS				RED BLOOD CELLS			HAEMOGLOBIN			SEDIMENTATION			RESULTS
Standard	Before	After	Present	Before Insulin	After Insulin	Present	Before Insulin	After Insulin	Present	Before	After	Present	
Insulin													
136	104½	115½	—	3,320	3,960	3,080	70	75	70	23	21	19	For one month all symptoms decreased. Indigestion disappeared; appetite improved; strength increased; cough and expectoration had practically disappeared; gained 11 lbs.; sputum positive. Developed symptoms of tuberculous enteritis. Refused to attempt supplementary feedings between meals, and ate very little at meal times. X-ray lesion stationary. Present: progressively worse; lost weight steadily. X-ray: Increased cavitation with increased fibrosis. Discharged as quiescent.
131	95	134	—	3,500	4,020	—	70	84	—	20	20	—	Disappearance of cough and expectoration; decreased appetite after two weeks, but increase after each increase in dosage. Weight retained during temporary intermissions. X-ray: contraction of cavity. Sputum negative. Discharged. Quiescent. Remained perfectly well until three months ago when had relapse following childbirth.
62 in.	92	106	—	3,920	3,280	—	74	70	—	19	9.8	—	During treatment had attacks of tonsillitis, with headache, nausea, vomiting and increased cough. Appetite improved; strength increased. Insulin discontinued temporarily; appetite would increase two or three days, and then remain stationary; weight was retained; occasionally had mild reactions; nervousness, increased hunger, perspiration, weakness disappeared promptly when food was taken. Gained 2½ lbs. after insulin was stopped. Discharged 12/12/32. X-ray: dcerease in infiltration, left. Sputum negative. General condition good. Present: has remained well.
122	94	99	too ill	3,120	3,040	2,940	60	65	60	None	22	24	All gastrointestinal symptoms decreased. No change in cough and expectoration; arrest in loss of weight. After insulin was discontinued, began losing weight; had lost 14 lbs. within 4 months. Present condition much the same. Clinically active. X-ray: increase in size of cavitation and consolidation in mid-third, left lung.
154	144	153	—	3,800	4,120	—	75	85	—	125	95	—	Indigestion disappeared; appetite improved; sense of well-being and increased strength. X-ray: developed cavity in right upper lobe. Unsuccessful attempts at artificial pneumothorax. Discharged 2/13/33. Continued to gain weight. X-ray: cavity, right, closed; cavity, left, 50 per cent smaller. Progressively improving; all symptoms except slight cough and expectoration have disappeared. Prognosis better than at any time since became ill.

TABLE 3—

NAME	SEX	AGE	CLASS	OPERATIONS AND COMPLICATIONS	SYMPTOMS	DURATION OF TREATMENT. MAXIMUM INSULIN DOSAGE
T. L.	M.	48	F.A.A.	Sinusitis	Loss of weight; anorexia; frequent sinusitis; loss of strength. Nausea and vomiting occasionally. X-ray: exudation bilaterally. Sputum positive.	6/11/32 to 9/10/32 U, xx, tid.
D. W.	F.	25	Min.	Artificial pneumothorax, 3/4/33	Patient 27 lbs. underweight, failed to gain. Appetite poor. No increase in strength. X-ray: exudative lesion, left. Sputum negative.	1/ 3/33 to 4/15/33 U, xv, A.M.: x, M. and P.M.
L. V. L.	F.	41	F.A.	Artificial pneumothorax, 10/15/31; pleural effusion February, 1932; until death, 6/13/33. Syphilis.	Night-sweats, pleurisy, fever 101°; loss of strength; loss of weight, 16 lbs. in 2 months. Severe anorexia. X-ray: cavity, right; exudative, left. Sputum positive.	11/26/32 to 1/24/33 U, xv, tid.
A. S.	F.	22	F.A.A.	Artificial pneumothorax, 2/11/30; phrenic neurectomy, 3/16/31.	Residence: 1st admission, about 18 months; discharged quiescent. Readmitted, July 13, 1932, 24 lbs. underweight. Symptoms of active disease. X-ray: bilateral, caseous. Sputum positive.	7/25/32 to 10/11/32 U, xx, tid.
M. K.	M.	7	M.A.A.	None: asthma.	Cough and expectoration; loss of weight; asthma. During residence, asthma worse; appetite very poor. Bilateral infiltration and enlarged tracheobronchial lymph nodes. Sputum negative.	9/ 6/32 to 2/22/33 U, x, tid.
A. T.	F.	28	M.A.	Sinusitis; tuberculous enteritis. Artificial pneumothorax, 2/13/32.	Emetic cough before breakfast; nausea and occasional vomiting. Indigestion; frequent attacks of sinusitis; fever, sputum positive. Left exudative; right caseous.	7/26/32 to 4/ 4/33 U, xx, tid.

Continued

WEIGHT IN POUNDS				RED BLOOD CELLS			HAEMOGLOBIN			SEDIMENTATION			RESULTS
Standard	Before Insulin	After Insulin	Present	Before Insulin	After Insulin	Present	Before Insulin	After Insulin	Present	Before	After	Present	
150	107	115	—	3,220	3,860	—	70	78	—	26.5	20	—	Discomfort from sinusitis disappeared; slight reactions, 6/28/32 and 7/14/32. On eighteenth day had large urticarial wheals, severe itching and burning: duration, 3 days. On 9/1/32 began to have languor, stuffy sensation. Insulin discontinued. Patient promptly began to improve. X-ray: increase bilaterally. Sputum positive. Died December, 1932.
129	104	112	—	4,000	3,500	—	80	75	—	None			Generally improved until began pneumothorax. Had some reaction to insulin, and pneumothorax. Began to lose strength, and felt generally worse. Insulin discontinued. Discharged 7/22/33. Apparently arrested. Continued pneumothorax; weight 110. Sputum negative. X-ray: left successful. General condition very good.
137	87½	89	—	3,260	3,560	—	70	75	—	27	27	—	For two weeks patient had increased appetite. No change in general condition; effusion increased. Increased symptoms with fever to 100°. X-ray: spread 1st and 2nd i.s. Sputum remained positive. Died 6/13/33 from air embolism following unsuccessful attempt to reëstablish pneumothorax.
101	79½	88½	—	3,420	3,820	—	70	70	—	26.5			Appetite improved slowly and steadily. Cough and expectoration decreased one-third in 2 weeks. Slight reactions from time to time; gained 11 lbs. After 2 months symptoms reappeared and became progressively worse. X-ray: no change. Sputum positive. After insulin discontinued, patient had steady progressive loss of weight. Died at sanatorium 3 months ago.
41	37	39	46	3,020	4,080	3,220	60	80	65	25	—	16	During first 3 months asthmatic attacks occurred less frequently; strength improved; appetite improved. Gained 9 lbs. After 3 months asthma became very severe. Appetite poor; lost 7 lbs. X-ray: stationary at present; condition unchanged.
139	102	116	—	3,460	3,600	—	70	70	—	20	22	—	Gastrointestinal symptoms almost disappeared; marked improvement in sinusitis (attacks less frequent); cough and expectoration decreased. Developed pleurisy with effusion. All symptoms reappeared, and patient became progressively worse; lost 10 lbs. After insulin was discontinued patient developed intestinal tuberculosis. Sputum always positive. X-ray: spread, right upper lobe. Died following discharge.

TABLE 3

NAME	SEX	AGE	CLASS	OPERATIONS AND COMPLICATIONS	SYMPTOMS	DURATION OF TREATMENT. MAXIMUM INSULIN DOSAGE
W. D.	F.	26	F.A.	Chronic tonsillitis. Attempted artificial pneumothorax, 6/13/31; phrenicectomy, 1/10/33.	During 14 months of residence patient had made no progress. Clinically, X-ray revealed increase bilaterally. Sputum positive. Clinically inactive.	8/13/32 to 1/10/33 1/10/33 to 1/24/33 U, xv, A.M. and P.M.
M. P.	F.	25	F.A.	Artificial pneumothorax; phrenicectomy, 5/24/34.	During residence patient made no progress. Weight was fluctuating within a six-pound range. Bilateral disseminated fibrotic lesion. Sputum negative.	8/13/32 to 1/13/33 U, x, tid.
J. McD.	F.	28	M.A.	None	Severe anorexia; weight remained 30 lbs. below standard. X-ray: exudative type above 3rd rib and tuberculosis bilaterally. Sputum negative.	5/14/32 to 7/ 9/32 8/14/32 to 9/ 2/32 U, xxx, tid.
M. B.	F.	48	M.A.	Phrenic neurectomy, 7/21/31; artificial pneumothorax, 12/5/31.	Severe anorexia; epigastric pain with nausea and vomiting; progressive loss of weight and strength. Low-grade fever. Cough and expectoration severe. Sputum positive. X-ray cavity not closed. Negative for ulcer or tuberculous enteritis.	8/31/32 to 9/11/32 11/ 4/32 to 11/28/32 U, x, tid.
E. M.	F.	28	F.A.	Artificial pneumothorax, November, 1931; pleural effusion, January, 1932; phrenic neurectomy, 3/20/33.	Fluctuating weight; indigestion, anorexia; nausea; languor; low-grade fever; all gastric symptoms increased first weeks; later disappeared. Strength increased; sputum decreased from 4 to 2 oz. Insulin discontinued temporarily. All gastric symptoms reappeared. Lost 2½ pounds. X-ray: cavitation, right. Sputum positive.	8/ 8/32 to 2/17/33 U, xx, tid.
H. T.	M.	23	F.A.A.	Artificial pneumothorax, unsuccessful, 7/23/32; phrenicectomy, 8/9/32; amputation small toe and metatarsal, 8/16/32.	Severe cough; profuse expectoration; languor. Large superficial tuberculous ulcer under left small toe. Partial sensory and motor paralysis. Loss of weight, 15 lbs. Bilateral infiltration. Cavity left upper lobe. Sputum negative.	7/23/32 to 8/ 9/32 8/12/32 to 8/16/32 8/24/32 to 11/18/32 12/ 2/32 to 1/24/33 U, xx, tid.

Continued

WEIGHT IN POUNDS				RED BLOOD CELLS			HAEMOGLOBIN			SEDIMENTATION			RESULTS
Standard	Before	After	Present	Before Insulin	After Insulin	Present	Before Insulin	After Insulin	Present	Before	After	Present	
Insulin													
140	113½	122	100	3,000	3,000	3,320	55	60	65	26	26	17	Increased appetite; general condition improved. X-ray: development of cavity, left upper lobe. Sputum positive. General condition same until had haemorrhage, 6/5/33; selective thoracoplasty recommended prior to haemorrhage; would not consent until year later. Present: sputum negative; is being given increased amount of exercise; cavity apparently closed; weight stationary since operation.
127	111	114	102½	3,680	3,460	3,000	—	70	60	29	28	28	Appetite improved for few weeks; then remained stationary. X-ray: progressive fibrosis. Sputum remains negative. Present: steadily losing weight; increased cough; progressive loss of weight.
121	91	103	92	3,240	None	3,240	65	None	70	None	196	17	Lesions had become fibrous. Weight would not increase; during treatment general feelings improved; appetite increased. On 6/19/32 patient had insulin shock; was unconscious for approximately 15 minutes; responded promptly to intravenous glucose; no other reactions during treatment. From 7/9/32 to 8/19/32 lost 5 lbs. Seen in clinic, March, 1933, weight was 86. Readmitted April, 1934. X-ray: improvement. Some change in weight might be attributed to extreme poverty. During residence has failed to gain weight.
138	108	110	—	3,120	3,640	—	68	75	—	—	—	—	Indigestion and epigastric pain; anorexia decreased; nausea and vomiting less frequent. On 8/20/32, diffuse urticaria, arms and legs for 3 days; itching plus burning. Sputum continued positive. X-ray: increase in size of cavities bilaterally. Patient discharged 3/31/33. Died approximately one month later.
119	94	104	89½	3,180	3,900	2,800	60	75	70	165	14	14	Patient was progressing most favorably; was given increased exercise and developed a recurrence of symptoms. During period insulin was discontinued, patient lost 2½ lbs. Developed symptoms of tuberculous enteritis; lost all weight gained. X-ray cavity smaller; decrease in infiltration. Pleural effusion, small quantity. Present: general condition same.
142	145	147	—	3,580	3,920	—	75	75	—	24	21	21	Insulin was interrupted several times, both for operations and to study any change in general feelings and symptoms. All symptoms continued to decrease. Gain in weight continued; gained 3 lbs. after permanently discontinuing insulin. X-ray: cavity closed; decreased infiltration. Sputum negative. Discharged six months ago. Has reactivation of disease with cavity in left upper lobe. Sputum positive.

TABLE 3

NAME	SEX	AGE	CLASS	OPERATIONS AND COMPLICATIONS	SYMPTOMS	DURATION OF TREATMENT. MAXIMUM INSULIN DOSAGE
J. V. H.	F.	25	F.A.A.	Artificial pneumothorax, 8/27/32; phrenicectomy, 11/1/32.	Had tuberculous pneumonia of 3 months duration. Anorexia; nausea; all symptoms of tuberculous enteritis. Temperature 100°; abdominal tenderness. X-ray: bilateral tuberculosis; caseous pneumonia, right. Sputum positive.	7/20/32 to 2/ 8/33 U, xx, tid.
L. J.	F.	24	M.A.A.	Artificial pneumothorax, 7/9/32	Severe anorexia; moderate nausea; annoying hacking cough. Fever to 100°F. Loss of strength and weight several weeks prior to admission. Sputum positive. X-ray: apparently 35 per cent cavity in 2nd i.s.; infiltration, remainder of lung.	7/30/32 to 11/25/32 U, xx, A.M. and xv, M. and P.M.
R. W.	M.	24	M.A.A.	Appendicectomy prior to admission. Artificial pneumothorax, 5/17/33. Syphilis: Kahn, 3-plus.	Very severe abdominal pains, with nausea and vomiting; anorexia; indigestion. Sputum negative. X-ray: bilateral finely disseminated type of infiltration.	7/30/32 to 8/25/32 U, v, tid.
E. C.	F.	30	F.A.A.	Artificial pneumothorax, 9/8/30 and 7/8/31; phrenicectomy, 5/19/31; thoracoplasty, 1st stage, 2/22/32.	During 20 months' residence general condition remained same; appetite poor; patient was languorous and apathetic. Cavity in left lung remained open. Sputum positive.	5/31/32 to 7/19/32 U, x, tid.
E. M.	M.	37	F.A.A.	None	During 2½ years' residence had made no progress; worst symptom was emetic cough; in morning could very seldom retain breakfast. X-ray: bilateral cavitation. Sputum positive.	1/20/32 to 7/20/32 U, xx, tid.

2. Analysis of the cases failed to reveal any correlation of this abnormal assimilation with other clinical or laboratory features; in particular, there was no perceptible relation with age, sex, type of tuberculosis, extent of lung involvement, the presence or degree of pneumothorax, the

Concluded

WEIGHT IN POUNDS				RED BLOOD CELLS			HAEMOGLOBIN			SEDIMENTATION			RESULTS
Standard	Before Insulin	After Insulin	Present	Before Insulin	After Insulin	Present	Before Insulin	After Insulin	Present	Before	After	Present	
Too ill to be weighed	81	81	—	3,440	4,100	—	70	78	—	32	23	—	During first month of treatment patient improved. Abdominal symptoms decreased; appetite improved; nausea and vomiting disappeared; gained 3 lbs. After temporary improvement, all symptoms reappeared with greater intensity. X-ray: increase in size of cavity, right side; increased infiltration, both lungs. Sputum positive. Died 3/1/33.
124	109	108	112	3,760	3,640	3,020	75	70	70	18	185	11	No change in general feeling. Developed pleural effusion which later became empyema. After insulin was discontinued, patient lost weight very rapidly. After 3 months, condition improved, and continues to improve. Present weight 94 lbs. Sputum positive. X-ray: left, pneumothorax, 80 per cent collapse, cavity smaller; right, no change. Present: general condition same. Tuberculous empyema (left).
151	120	129	Dead	4,140	3,600	Dead	80	70	—	24.5	23	—	Appetite much improved; strength increased; apathy disappeared. Was being given antisyphilitic treatment; following each dose of neoarsphenamine, patient would have attacks of nausea, vomiting, headache. Would refuse all food. Insulin had to be interrupted several times. Gained 9 lbs. Following discontinuance of insulin, lost consistently for 2 months; then began to gain to maximum of 148. Signed release; had relapse; died 3 months ago.
126	107¾	113½	128	3,660	No	4,020	75	—	80	26	26	22	During first 17 days patient felt well; all symptoms decreased; later was nauseated; appetite poor; developed languor, lassitude and fever during postinsulin period; general feeling improved; nausea disappeared; gained 8½ lbs. Sputum remained positive; cavity partially closed; weight increased steadily.
153	108	119	Dead	3,380	4,000		60	80		25	22	Dead	During first four months of treatment all symptoms decreased. Disappearance of nausea and emetic cough most striking result. Gained from 108 to 119 lbs. Few minor reactions. After four months all symptoms increased; patient died 6/27/33.

blood-corpuscle count, the sedimentation rate, the presence of complications including suspicions of liver damage, the diet, the state of nutrition, exercise, the psychic condition, the prognosis as demonstrated by the subsequent course of the disease, or combinations of these factors.

3. The glucose test also is not helpful in selecting patients for insulin treatment or predicting the response to such treatment.

4. On the theoretical side the causes of the varying results of this test are unknown.

5. On the practical side, the test has no prognostic or other known significance.

B. Concerning Insulin Treatment

1. Insulin is not curative of tuberculosis and has not been so regarded at any stage of this work.

2. Our series of 134 cases is presented without analysis, in the belief that all such series must vary according to the types of cases and many individual factors, and it is not expected that any such publication can demonstrate a reduction of mortality by this method. The mortality in this series is high, representing the high proportion of severe or hopeless cases.

3. The above limitations apply likewise to bed-rest, light treatments, vitamine diets and other measures which are in widespread use, and our observations likewise indicate a genuine value of insulin when properly used in selected cases.

4. As in many diseases, certain symptoms may become harmful or dangerous in themselves, so also, in tuberculosis, anorexia or malnutrition may be sufficiently serious to require correction, and, in actual fact, it is the therapeutic practice everywhere to try to build up the weight and strength of such patients. This is preëminently the need which insulin fills, and in many instances it serves the purpose better and more powerfully than any method heretofore used.

5. In addition to the improvement of weight, there is commonly a tonic effect represented in improved strength, spirits and subjective well-being. On this account there may sometimes be also an economic advantage in greatly shortening the hospital stay of patients who are suffering chiefly from malnutrition.

6. While insulin is useless in the severest cases, it is rarely harmful or contraindicated, the principal obstacle being urticaria or allergic manifestations in a few instances. Under proper management insulin reactions are rare, and are harmless if they appear. Also, with experience and skill in the method a number of cases which at first appear unresponsive or incapable of gaining weight may be carried through successfully.

7. In general, therefore, since it is admitted that malnutrition is harmful in tuberculosis, the conclusion appears to follow that insulin under suitably chosen conditions is a valuable addition to the treatment.

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THE USE OF INSULIN IN TUBERCULOSIS

A Report of 13 Cases with a Review of the Literature[1]

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In spite of the advances made in recent years in the treatment of tuberculosis, rest and nutrition are still universally considered as the most indispensable factors in any therapeutic regimen. Gain in weight, along with drop in temperature, and disappearance of tubercle bacilli from the sputum are among the favorable indices of progress of the disease. Gain in weight, moreover, is an index of improvement that the patient himself can readily discern and understand. It is something that many patients look forward to, and, if anorexia is present, to cause malnutrition, the seriousness of the situation may be greatly exaggerated by the patient. The apprehension of the patient will militate against a wholesome, hopeful attitude, creating a vicious circle with more anorexia, "indigestion" and malnutrition.

Not only is anorexia a frequent symptom, interfering with the proper nutrition of the patient, but various types of "dyspepsias," with nausea, vomiting, pyrosis, distention, etc., are stumbling-blocks to the undernourished patient. These digestive symptoms are usually but poorly explained and more poorly treated. Such general terms as *toxaemia* are invoked as explanations, and both the toxaemia and malnutrition are allowed to carry the patient to his inevitable end. In other cases, a superimposed peptic ulcer is postulated. While it cannot be denied that these explanations are valid at times, in most cases we must look for the root of the trouble elsewhere. It is certainly worth while to look for more immediate causes of these troublesome digestive symptoms, for as a very prominent writer in this field (1) says, "The problems of diet and digestion are fundamentally important, and, therefore, too much care and trouble cannot be taken in their solution."

That the gastric symptoms in tuberculosis are not due to organic lesions, but rather to functional disturbances in motility and secretion, finds expression in such dependable sources as textbooks (2). In 1924 Kantor (3) wrote that the gastric symptoms were due to atony of stom-

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ach and stagnation of its contents; also probably to the accompanying anacidity or subacidity. It is only logical to assume that an attack on the basic dysfunction would bring more desirable and lasting results than mere symptomatic treatment with bitters and carminatives.

In the extensive studies of insulin since its discovery by Banting and Best in 1921, it has been found that it has numerous functions besides its direct action on carbohydrate metabolism. Quigley, Johnson and Solomon (4) showed that in man insulin has a marked effect on the motor activity of the stomach. They have shown that both the tone and the duration of activity are increased. Insulin seems to have a stimulating effect upon the motility of the entire gastrointestinal tract (5) (6), while dextrose seems to have an opposite effect. It is a common physiological fact that hunger is accompanied by increased gastric motility or fasting contractions of the stomach. The quick abatement of hunger by sweets (dextrose) may be due to depression of the hunger movements of the stomach.

That insulin has a specific effect on the gastric secretions has also been shown by a number of workers. Meyer (7) showed that insulin increased the acidity and secretion of the stomach, especially in gastric achlorhydria. The maximum effect was produced in his cases within 75 to 90 minutes. He further points out that the increase of stomach secretion is a symptom or integral part of the early hypoglycaemic state, and recommends insulin in the treatment of subacidity, anacidity, and anorexia. Among others who have pointed out that insulin increases gastric secretion are Musante (8) and Popesco and Diculesco (9). Lueder and Watson (10) claim that insulin causes a measureable increase in pancreatic secretion and attribute gains in weight to this improved secretion.

In diabetes, a disease most intimately connected with insulin deficiency, a high incidence of achlorhydria is found (11) (7). Kuehn and Witscher (12) also point out that the majority of severe diabetics have hypochlorhydria. This is directly attributed to a disturbed chlorine metabolism, dependent upon hypofunction of the pancreas. Ingram (13) is another investigator who has shown an absence of free hydrochloric acid in nine out of 13 diabetics examined.

That insulin is used with great success in the treatment of undernourished patients is borne out by numerous reports (14) (15) (16). The fate of diabetic, tuberculous patients before the insulin era was gloomy indeed. Even with the advent of insulin therapy, the tuber-

culous diabetic was treated with great caution and apprehension. Allen (17) was among the first to publish favorable observations concerning patients having a combination of the two diseases and treated with insulin. He noted that a tuberculous patient with diabetes showed a great increase in appetite and intake of food following the use of insulin. Another patient with low sugar-tolerance showed improved nutrition and a general diminution of infection.

Systematic use of insulin for the improvement of nutrition in tuberculous patients has been more popular among European workers and was probably initiated by Vogt and Falta. Hofhauser and Schoen (18) used insulin on 13 young patients with favorable results. Four showed gains in weight ranging from 3.3 to 5 kg. (7.25 to 11 lbs.), others showed marked increase in appetite with little gain in weight, and still others showed increase in appetite with no gain in weight. These workers see no contraindications to insulin, but in one case they discontinued it because of severe haemoptysis.

Zelter (19) also reported favorably upon the use of insulin in 10 tuberculous patients, and concluded that it is an important therapeutic agent in the treatment of undernourished tuberculous patients. Insulin, according to him, influences the utilization of all the foodstuffs. The blood-sugar was lowered, showing a better utilization of carbohydrates. Marked fluctuations in blood-sugar were not noted, and severe symptoms of hypoglycaemia were not observed. This worker feels that this mode of treatment does not stir up complications, and he does not agree with Herich (20) that insulin causes excessive water-retention. Zelter treated this group of patients for three to four weeks. He began with 5 units per day, and gradually increased this dose to a maximum of 60 units per day in divided doses. Gomez and Breton (21) feel that the emaciated tuberculous patient can be treated with confidence by means of insulin, but they caution against hypoglycaemia and believe in small doses never exceeding 30 units per day. They prefer to give insulin for two weeks and stop it for two weeks, three such courses being sufficient. More recently Allen (22) reported favorable results from the use of insulin in nondiabetic tuberculosis patients. He deviated from the usual tenets in this treatment by the use of much larger doses of insulin and over a much longer period (eight months). Some of his patients responded very readily and favorably, while others showed little or no response, but the exact numbers of each are not stated.

The mechanism by which insulin causes a gain in weight is not purely

by increasing the appetite and consumption of food, but also by aiding the storage and redistribution of nutrient materials. Insulin definitely aids glycogen-storage and holds back 3 gm. of water for every gram of glycogen stored, thus aiding hydration in dehydrated toxic patients (23). Insulin also lowers the fat in the blood, not by oxidation or by storage in the liver, but by storage in the connective tissues (23). Besides the effect on the general food-metabolism, insulin, as has been previously pointed out, has an effect on the motility of the gastrointestinal tract and its secretions.

There is evidence (24) (25) to show that in various infections and toxaemias there is a decrease of dextrose-tolerance, which may be due to either the suppression of insulin secretion or an inhibitory effect on insulin action. From a clinical point of view, it may be assumed that in tuberculosis there is a suppression of insulin secretion along with other gastrointestinal secretions, rather than an inhibition of insulin action. This latter assumption is upheld by the fact that an insulin reaction was produced in one of our patients by 5 units of insulin. The administration of insulin in tuberculous patients may then replace this pathological deficiency.

Our series of 13 cases were selected on the following basis: The patients had to show a combination of loss of weight and anorexia, together with dyspeptic symptoms. There were a few cases that did not complain of anorexia, but did complain of various gastric symptoms. It was surprising to see how few of the many far-advanced cases at the Cook County Hospital Tuberculosis Service complained of anorexia. We felt that to put on insulin a patient who did not complain of anorexia, and stated that he ate all the food he received, would be illogical, since the paramount subjective effect of insulin is an increase of appetite.

Among these cases there were 3 men and 10 women. All the men were white, and all but one woman were colored. Twelve cases fell into the far-advanced group, and most of them had a hopeless prognosis. Seven of the cases observed died. The reason for selection of such poor patients from the prognostic point of view was threefold: (1) we wanted to see what influence this treatment will have on this type of patient; (2) the majority of patients complaining of anorexia were in this group; and (3) most of the patients on the service were colored, and were far advanced on entrance.

At first it was hoped to make a correlation between gastric acidity and gastric symptoms. Although some interesting observations were

made in this direction, it could not be carried to its ultimate conclusions, because of the refusal of the patients to coöperate.

Cases

1: H. L., colored, female, aged 17. The patient was ill for one year. Classification, far-advanced, pulmonary tuberculosis. Had diarrhoea, thought to be due to gastrointestinal tuberculosis, temperature to 102°, and sputum positive. In addition, complained of severe anorexia and was rapidly going downhill. Weight on entrance, June 30, 1934, was 86½ lbs.; usual weight around 115 lbs.; weight declined to 69¾ pounds on August 24; between September 21 and October 6, 1934, too ill to be weighed. Beginning October 3, 1934, insulin, 5 units three times a day, half an hour before meals, was started. That same day patient felt somewhat dizzy and faint, but reported marked improvement of appetite. Two days later, patient was still dizzy at times following insulin administration. Three days later the insulin was stopped because the patient was too weak and could not help herself with the food, and an insulin reaction was feared. Patient's appetite was reported as good for about two weeks after insulin was discontinued. Later the anorexia recurred, the general condition of the patient became poorer, and she rapidly failed and died at the end of October.

2: P. F., colored, female, aged 22. Tuberculous infiltration in both lungs, with cavitation in left; temperature to 101°; sputum positive; nausea, vomiting and anorexia also complained of. Weight on entrance, June 6, 1934, 75½ lbs.; decreased to 67 lbs. on October 5, 1934; patient about 35 lbs. underweight on entrance. Insulin, 5 units three times a day, one-half hour before meals, begun on October 3, 1934. The following day appetite was reported improved and no untoward reaction was noticed. About a week later appetite reported as very good; whereas, before, the patient did not even eat the regular ward diet, at this time she consumed a great deal of food brought in from the outside. Two weeks after insulin was started, she showed a gain of ¾ lb., ate her food with relish, and was no longer nauseated. At beginning of December, although her appetite continued better, she began losing ground, the pulse became very rapid, 120 to 144, and temperature rose to 101.2°. Because of general condition of patient the insulin was stopped. Although her appetite continued improved for some time, her general condition became steadily worse and she died early in January.

3: W. H., colored, female, aged 39. Bilateral far-advanced pulmonary tuberculosis, with pleural effusion on left side. Patient also complained of hoarseness, shown to be due to tuberculous laryngitis, on laryngoscopic examination. In addition, complained of the following gastrointestinal symptoms: anorexia

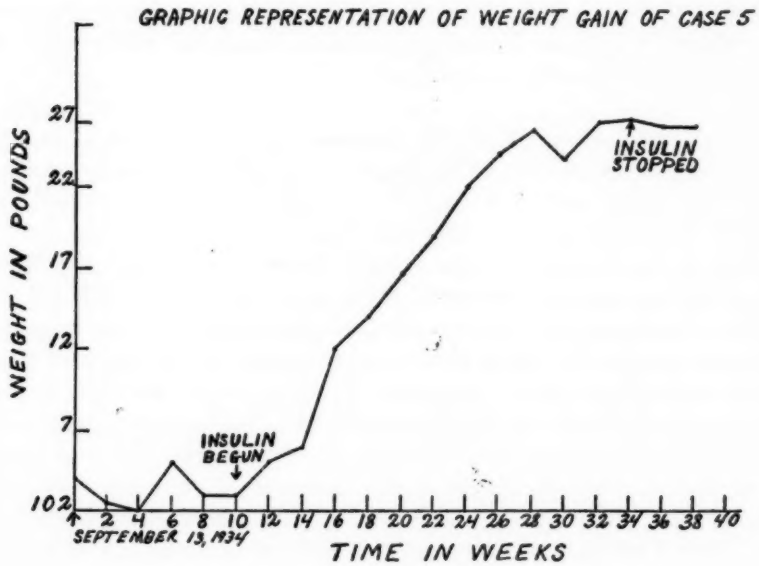
of one month's duration and very severe in type; also eructations, epigastric discomfort and nausea. The patient lost about 30 lbs. before entrance to the hospital, and 4 lbs. in ten weeks during hospital stay; weight was 86¾ lbs. at beginning of observation. On October 3, 1934, Ewald meal showed: free acidity, 0; combined acidity, 40. Blood-sugar, 93 mgm. per 100 cc. of blood. The following day the patient was put on 5 units of insulin, t.i.d., one-half hour before meals. No reaction occurred and the appetite was reported improved. Two days later appetite so markedly improved, that patient asked for another serving of food about 8 P.M. Several days later marked dyspnoea developed and 900 cc. of fluid was removed from left pleural cavity. Patient gained one pound in the first two weeks of insulin therapy, in spite of the removal of the large quantity of fluid. Meanwhile, her extrapulmonary tuberculosis was getting worse. The diarrhoea became troublesome; and phonation and deglutition were painful, so that the improved appetite was very painfully satisfied. Hence, the insulin was stopped, November 14, 1934. Several months later the patient died.

4: C. A., female, colored, aged 28. Bilateral far-advanced pulmonary tuberculosis with cavitation. Sputum positive. Complaint of anorexia, nausea, abdominal cramps and diarrhoea for two months. Loss of 25 lbs. before entrance to hospital, July 20, 1934, and 8 more pounds since entrance. Temperature to 101.6°. On October 3, 1934, Ewald meal yielded: free acidity, 6 and total acidity, 42. Blood-sugar, 93 mgm. per 100 cc. of blood. The following day the patient was put on 5 units of insulin, t.i.d. The patient was markedly emaciated. Anorexia was almost complete, the patient refusing most of her meals. On the same day, following the second dose of insulin, patient refused her meal. About one and one-half hours after administration of the insulin the patient became weak and nervous, twitching of localized muscle groups occurred, and the patient promptly lapsed into coma. Two hundred cubic centimeters of milk was administered by gastric gavage. Soon after this the patient recovered consciousness, and asked for food to satisfy a ravishing hunger. On this occasion she ate at least twice as much as an average person eats at one meal. The appetitie continued very good after this, the patient waking in the middle of the night asking for food to satisfy her enormous appetite. Because of the very large amount of food ingested, the diarrhoea became aggravated and the insulin was discontinued October 10, 1934. The patient died November 2, 1934. Postmortem findings included bilateral caseous pulmonary tuberculosis, with large cavities, and also tuberculous ulcerations of the ileum.

5: M. B., white, female, aged 45. Moderately advanced tuberculous infiltration of both upper lobes, of many years' duration. Discharging old empyema

wound. Sputum positive, once in November 1934, and negative at all other times. Temperature normal. The patient, in addition, complained of extreme anorexia for three months; also nausea, vomiting, and occasional diarrhoea for two months. Further stated that she had nausea, vomiting, and occasional abdominal pains for a number of years. These symptoms were irregular in their occurrence and unaltered by time. On October 4, 1934, Ewald meal yielded: free acidity, 0, and total acidity, 35. The following day this patient was started on insulin, units 5, t.i.d. one-half hour before meals. On October 17, 1934, the dose was raised to units 5–10–10 before the respective meals of the day, because patient still complained of anorexia. In spite of no apparent subjective improvement, patient gained 2 lbs. in the first

GRAPH 1



two weeks, whereas before she had been losing weight for months. She steadily gained weight and, with the exception of several small haemoptyses, kept on improving. After about a month to six weeks, she reported feeling much better. The gastric symptoms were allayed, the appetite was excellent, and the previously pessimistic outlook became hopeful and cheerful. Against a steady decline in weight for some ten months, we obtained a gain of 24 lbs. in less than five months without any special diet. (See graph 1 and table 1.) As a matter of interest, it should be stated that the diet was below average in quality. The weight gained was retained during a six-week period of observation following the discontinuance of the insulin. The patient left the hospital looking and feeling well and with a very hopeful attitude.

6: E. B., colored, female, aged 25. Far-advanced bilateral pulmonary tuberculosis, with night-sweats, cough, pain in the chest, loss of weight, and anorexia. On October 11, 1934, Ewald meal yielded: free acidity, 26, and total acidity, 51. The following day the patient started on units 5 of insulin, t.i.d., which was raised to 10 units, t.i.d., five days later. No reactions were noted at any time. About one week after beginning the insulin her appetite was definitely better, but the patient complained of some pleural pain. The appetite stayed improved, and she kept on gaining weight till it was above

TABLE 1

Changes in weight of case 5

DATE	WEIGHT	REMARKS
1934	*lbs.*	
January 13	108¾	
July 13	104	Little variation
July 27	102½	
August 10	102	
August 24	105	
September 21	103	
October 6	103	Insulin begun
October 19	105	
November 2	106	
November 17	112	
November 30	114	
December 15	116¾	
December 28	119	
1935		
January 11	122	
January 25	124	
February 9	126½	Patient went home for 3 days
February 21	123¾	
March 3	127	
March 24	127¼	Insulin stopped
April 6	126¾	
April 15	126¾	

her maximum normal point. She gained 16½ lbs. in three months on a diet hardly conducive to gaining weight. (See table 2 and graph 2.) It should also be noted that the insulin was stopped for about two weeks, about one month before the end of the observation, and in those two weeks no gain in weight was noted. When the insulin was reinstated an increase of 5 lbs. occurred.

7: F. R., colored, female, aged 26. Moderately advanced pulmonary tuberculosis, with infiltration of upper half of left lung field. Sputum negative. Temperature to 101°F. Symptoms included loss of 30 lbs., weakness for six

months, and anorexia. Ewald meal yielded: free acidity, 0, and total acidity, 12. The following day, October 10, 1935, the patient was put on insulin,

GRAPH 2

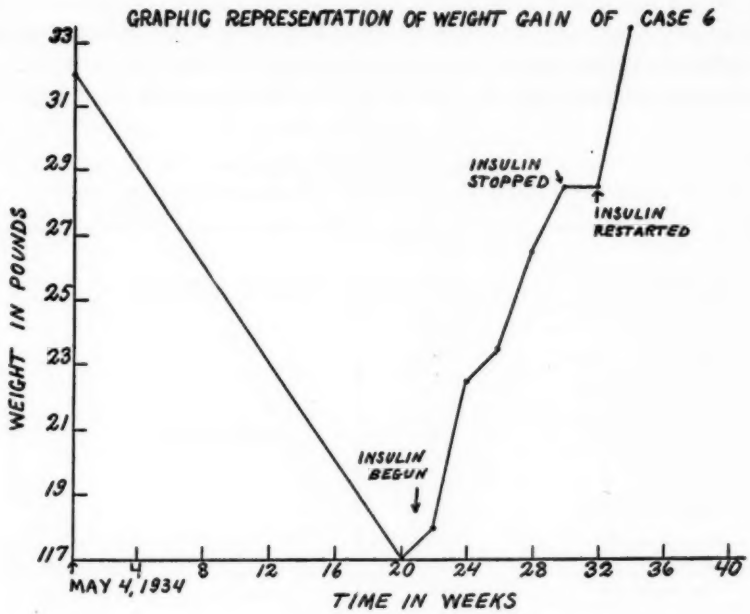


TABLE 2

Changes in weight of case 6

DATE	WEIGHT	REMARKS
1934	*lbs.*	
May 4	132	
October 6	117	Steady loss of weight
October 12		Insulin begun
October 19	118	
November 2	122½	
November 17	123½	
November 30	126½	
December 15	128½	Insulin stopped
December 28	128½	Insulin restarted
1935		
January 15	133½	

5 units, t.i.d., but, because her appetite was only slightly improved, this was changed three days later to 5 units in the morning only, and the other two

doses were doubled. This patient was on pneumothorax treatment and, October 16, a refill was attempted, but was found impossible, due to a high positive pressure caused by pleural effusion on the left side. The following day the patient became very dyspnoeic, the heart was displaced to the right, and the pulse very rapid and thready. Thoracentesis was done, with the removal of 1500 cc. of straw-colored fluid. At this time circulatory embarrassment became evident. The cardiac dulness and shadow were displaced to the right, and oedema of the face and dependent parts were noted, and the pulse-rate rose to 140; but, in spite of this turn for the worse, the patient reported improved appetite. On October 19 she weighed 125 lbs., 8 lbs. more than previously, but this change in weight was due to oedema. The patient was put on digitalis and diuretics. On October 24, 2000 cc. of fluid was again removed from the left pleural cavity, and, although slight improvement occurred, the heart was still displaced, and there was considerable dyspnoea and some oedema. The temperature was as high as 102°F. during this time. On November 1st the weight declined to 115 lbs. By November 30, the oedema disappeared completely, the temperature fell to normal, pulse and respiration decreased in frequency, and the weight declined to 107½ lbs. It should be remembered that the patient's condition during this period was critical. At this point the patient began gaining weight and strength, but the pleural effusion persisted, with a compensated cardiorespiratory mechanism. Appetite was very good, and the patient weighed 117½ lbs., March 6, 1935, but because the weight gain became retarded (that is, one pound in the last six weeks and 9 lbs. in the previous seven weeks) the insulin was stopped in order to observe what would happen. The results were as follows: The good appetite persisted, and the patient gained 10 lbs. more in two months.

8: J. McN., male, white, aged 45. Far-advanced pulmonary tuberculosis, bilateral. Patient lost 30 lbs. or more before entrance to hospital, July 31, 1934: at that time he weighed 120 lbs. Patient was unable to eat, and make use of his fair appetite because of belching, pyrosis, and "poor digestion," slight epigastric distress, nausea and vomiting, all of which began soon after ingestion of food. On September 28, 1934, his weight was 118½ lbs. On October 11, 1934, Ewald meal yielded: free acidity, 44, and total acidity, 82. The following day the patient was put on 5 units of insulin, t.i.d., and the day after this the patient reported that appetite was better and pyrosis and epigastric distress greatly decreased. The last two daily doses of insulin were increased to 10 units each. On October 26, the patient had a slight insulin reaction, apparently because his meal was served too late. His weight at this time was 117 lbs., but he was weighed with fewer clothes on. On October 29, the patient had blood-streaked sputum and complained of nausea

and anorexia. The following day he died suddenly from a massive haemoptysis.

9: J. S., male, white, aged 33. Far-advanced bilateral pulmonary tuberculosis, with positive sputum. Patient very emaciated; appetite very poor for three weeks; pyrosis very troublesome; also nausea, bloating, distention and belching. Weight down from 137 lbs. on June 10, 1933, to 110 lbs. on June 2, 1934. On October 19, 1934, it was 113 lbs., the normal being around 170 lbs. On October 11, 1934 Ewald meal was given, but no material could be aspirated in 40 minutes. The following day patient was started on 5 units of insulin, t.i.d., one-half hour before meals. Two days later, although appetite was improved, the dose was raised to 10 units before the last two meals. On October 17, patient was put on 10 units of insulin, t.i.d. On the second day after this new dose was initiated, the patient had a slight insulin reaction. Pyrosis, nausea, and all epigastric symptoms subsided, and the appetite became voracious. Beside eating the meals served, the patient ingested much other food. On one particular occasion, we observed the patient consume, in addition to his regular supper, one pound of cold meats, with bread, a piece of cake and pie. In spite of this excellent appetite his weight on November 1, a little over two weeks after the initiation of the insulin, was only 114 lbs., and after that the patient began losing weight. On November 28, the insulin was discontinued and the weight was only 110 lbs. Although the appetite continued improved and the epigastric symptoms were practically abolished till the end of December, the patient kept on declining, and died in the middle of February, 1935.

10: P. Q., white, male, aged 53. This patient had a history of pulmonary tuberculosis dating back seventeen years. His involvement was far-advanced and bilateral, but not very active. He was suspected of having, in addition, gastrointestinal tuberculosis. This patient was put on treatment because he lost weight and complained of nausea, "sour belching" and epigastric pressure for one year. His appetite was fair but he could not eat much at a time. On October 14 the patient was put on 5 units of insulin, t.i.d. Since no increase in appetite was reported after four days the dose was increased to 10 units, t.i.d. The patient had a slight insulin reaction on the morning of the increased dose. Digestion was reported as better before the dose was increased, and appetite was notably improved about one week after the larger dose was begun. The patient's weight was 101 lbs. on August 31, 1934, and only 98 lbs. on October 12, 1934. On October 26, twelve days after the beginning of the insulin therapy the weight increased to 101½ lbs. Several days later, the insulin was stopped on the request of the patient. He attributed the death of another patient under treatment to its use. On November 22,

the patient's weight was down to 99 lbs. This would probably have been a favorable case if the treatment had been continued.

11: L. M., colored, female, aged 21. Far-advanced pulmonary tuberculosis with bilateral cavitation. Patient entered the hospital with an acute pneumonic phthisis. Sputum was positive. This patient lost a good deal of weight and complained of anorexia. The patient was put on insulin, units 10, b.i.d., noon and evening, on November 17, 1934. The appetite was improved after about a month, but no gain in weight occurred. On December 28, five units of insulin were begun to be administered, also in the morning. On January 20, 1935, the insulin was stopped because the patient became acutely ill, with high temperature, and signs of consolidation at the right base suggestive of pneumonia. On March 8, 1935, she was weighed for the first time after her recent set-back, and it was found to be 94 lbs. Two weeks later, because her weight came down to 90½ lbs., she was put on insulin, 10 units, b.i.d., before the noon and evening meals. After this her weight began increasing, until a gain of 6½ lbs. occurred. At that point the gain became very slow; therefore, the insulin was stopped, and a further increase in weight occurred. (See table 3.)

TABLE 3

Résumé of progress of case 11

DATE	WEIGHT	REMARKS
	lbs.	
6/20/34	107½	Weight oscillating with very small variation
11/16/34	107¾	
11/17/34		Insulin begun u-x-x
11/30/34	107	
12/27/34	105½	Insulin u-v-x-x
1/11/35	107	
1/20/35		Pneumonia, Ins. stopped
3/ 8/35	94	1st wt. since illness
3/24/35	90½	Insulin u x b.i.d.
4/ 6/35	93	Insulin u x b.i.d.
4/20/35	96¼	Insulin u x b.i.d.
5/ 3/35	96½	Insulin u x b.i.d.
5/17/35	97	Insulin stopped
5/31/35	99½	
6/14/35	101	

12: V. H., colored, female, aged 17. On entrance to the hospital, October 15, 1934, the patient was thought to have a moderately advanced tuberculous process in the right upper lobe. Temperature was 103°F., out of proportion to the findings. Pneumothorax was instituted, but soon stopped because the

patient appeared to be getting worse. Roentgenogram, one week after entrance, showed cavitation and consolidation of upper half of right lung. The onset dated back to a month before entrance, and there was also a history of a brother having died from tuberculosis. Insulin was started because the patient had anorexia and was losing weight while in the hospital. The patient's weight fell from 103 to 92 lbs. during two months of hospital stay. On December 28, 1934, she was put on 5 units of insulin, t.i.d. On January 11, 1935, her weight was 91½ lbs., but her appetite was improved. Four days later the noon dose of insulin was increased to 10 units. But, in spite of this, two weeks later the weight had decreased another pound to 90½ lbs. On February 8, 1935, her weight was 87½ lbs., the temperature was very high, the patient was very toxic, the physical findings were scattered throughout the right lung and part of left. The insulin was then stopped because the patient was vomiting and rapidly going downhill. The patient died March 17, 1935, from a rapidly progressing phthisis.

13: J. B., colored, female, aged 25. Far-advanced bilateral pulmonary tuberculosis, with X-ray findings of dense infiltration throughout both lung fields. Sputum showed tubercle bacilli on one occasion. Temperature low-grade, to 100°F. Entered the hospital on March 5, 1935, with weight of 98 lbs.; usual weight was about 25 lbs. above that. Appetite was very poor. On March 24, put on insulin, 5 units, t.i.d. On April 6, weight was 96 lbs., the patient not having been weighed since her entrance. Her appetite was much better. She stated that she was hungry most of the time, not getting enough to eat, whereas previously the food that she received was in excess of her needs. On March 20, because her weight was only 95¼ lbs., the insulin was increased to 10 units before the first two meals of the day. Appetite remained excellent, but in spite of that weight decreased slightly to 94¾ lbs. on May 18, when the insulin was stopped. On May 31 the weight shot up to 98 lbs., and the weight two weeks after that was 100½ lbs.

DISCUSSION AND CONCLUSIONS

This group of cases and the conditions under which they were observed are peculiar for several reasons. They were all, with one exception, far-advanced cases, many of which died. No adjustment or change of diet was made which could be thought to be a contributing factor in the change in weight or the improvement in appetite. No special precautions were taken to avoid insulin shock, except to tell the patient to have an orange or a piece of candy around, in case the meal were delayed, and not to abstain from the entire meal but to take at least one glass of milk, in case of a possible lack of appetite.

That insulin is not a "cure" for tuberculosis is obvious, but it is equally obvious that it is effective in stimulating appetite and allaying certain gastric symptoms so frequently complained of by the tuberculous patient. All the patients reported improvement in appetite, which was very obvious in many cases in which the appetite bordered on gluttony. When a patient wakes up in the middle of the night asking for food, it is not mere fancy. As a matter of fact, one patient (case 5) was unwilling to admit an improvement in appetite, but her weight kept on climbing. All the patients received bitters, carminatives, and alkalies to improve their appetite and their gastric symptoms before the insulin was started, but no results were obtained. One peculiar thing was noticed; namely, that there is no parallelism between the relative improvement in appetite and the gain in weight. The two best cases, as far as gain in weight was concerned, were cases 5 and 6, but they did not seem to have a voracious appetite. Cases 3 and 9 seemed to have a voracious appetite, but did not gain weight.

As to the *modus operandi* in producing the improved appetite and gastric symptoms, we believe it is by means of improved gastric tone and motility, and increased or better balanced secretion. Although we could not draw any valid conclusions about the latter, because of insufficient data, yet four of the 6 patients on whom gastric analyses were done showed none or very low free acid.

Gain in weight was rather capricious. All those that did not gain any weight died. This was interpreted as meaning that the pathological process was very active, and defensive reactions completely broken down in these cases, at the stage at which the insulin was started. A few patients (cases 7 and 11) suffered a set-back during the course of treatment, depending upon their pathological process, which interfered with favorable results, but as soon as the complications subsided the patients began to gain weight. It should be noted that case 7 continued with the insulin when she was extremely ill, and her appetite remained good. It is more than probable that this favorable feature was enough to tip the scales in her favor when her life was in the balance. Another peculiar feature noticed in several patients (cases 7, 11 and 13) was that a gain in weight was noted after the insulin was stopped.

Concerning the dose which was rather small and not of wide variation, varying from a minimum of 5 units, t.i.d., to a maximum of 10 units, t.i.d., it is doubtful whether a larger dose would have influenced more favorably the cases that did not gain any weight. As a matter of fact,

these far-advanced cases could not tolerate a very large dose. The toxaemia in tuberculosis apparently does not interfere with insulin function. One of our cases went into insulin shock from 5 units of insulin (case 4), and several others had mild reactions. The severe reaction of the above case was attributed to the total lack of glycogen reserve in the liver, produced by the prolonged malnutrition. Even the above reactions could have been avoided if the patients would have carried out their instructions. Therefore, we feel that with this moderate dose the treatment can be carried out at home by a fairly intelligent patient.

The indications for the use of insulin are anorexia and loss of weight along with the frequently accompanying epigastric symptoms. There is no point in using insulin when the patient is gaining weight, even though he may complain of an unsatisfactory appetite. It may be worth while, occasionally, to use insulin in a patient losing weight, in spite of an apparently good appetite. Although the insulin may cause no subjective change in a case like this, it might cause a gain in weight by aiding glycogen- and fat-storage (23).

The contraindications against the use of insulin are few. No untoward effect was noticed that could be attributed directly to insulin, except the occasional avoidable insulin reaction. However, we feel that real contraindications against the use of insulin are (1) laryngeal tuberculosis when swallowing is painful; (2) gastrointestinal tuberculosis with diarrhoea, because increased ingestion of food aggravates and increases the diarrhoea; and (3) extreme emaciation and exhaustion, when the patient needs help in feeding and when an insulin reaction is more likely to occur and be more severe.

SUMMARY

1. Insulin therapy was used in 13 patients, all of them, with the exception of one, suffering from far-advanced pulmonary tuberculosis.

2. The dose varied from 15 to 30 units a day.

3. No attempt was made to modify the diet.

4. All the patients showed improvement in appetite and improvement in gastric symptoms.

5. The highest gain in weight was 24 pounds. All of the patients had been losing weight prior to the beginning of this treatment.

6. All of the patients that did not show any gain in weight died during the observation.

7. Several patients gained weight up to a certain level and then became stationary; upon withdrawal of the insulin they began to gain again.

8. There is no contraindication to the use of insulin except when the patient is unable to avail himself of more food because of pain in swallowing, diarrhoea or extreme exhaustion.

9. There is one disadvantage, namely, the need of using it hypodermically.

10. The conditions of this observation were such that they can be duplicated in home treatment.

11. It is believed that the therapeusis of the insulin action is based on improvement of gastric motility and secretion, and the storage of glycogen in the liver and fat subcutaneously.

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HIGH CARBOHYDRATE DIETS IN PULMONARY TUBERCULOSIS

ELLIS B. FREILICH AND GEORGE C. COE[1]

Since the study of nutrition and dietetics was incorporated into the practice of medicine, our concepts of dietary treatment of disease have changed. Evidences of this are present in the newer dietetic management of the nephritides, hypertension, diabetes, obesity, gastric ulcer, etc. In the field of tuberculosis, a definite and marked change has taken place. The ability of the patient to store fat was once thought to be the best criterion of progress. It is now known that from a nutritional standpoint the greatest good for the tuberculosis patient can be best accomplished by a liberal, but not too liberal diet, aiming, not toward obesity, but toward the so-called "ideal weight."

Many perplexing and uncertain problems present themselves in studying the effect of diet on tuberculosis. Heretofore, it was generally thought that a high caloric intake derived from a well-balanced diet was in itself satisfactory. Today, such necessary adjuncts as codliver oil and calcium are needed to supplement the mineral and vitamine content of the daily diet.

A short time ago insulin was generally introduced into the treatment of tuberculosis patients in an effort to increase weight and nutrition. We now know that it must be used, not indiscriminately, but with individual consideration for each case.

Tuberculosis may be considered as a chronic infectious process, with fever and an increased metabolism as its principal characteristics, and with undernourishment as a frequent consequence. The metabolism in tuberculosis is affected, on the one hand, by the fever and the infectious process, and, on the other, by the diet and the nutrition of the patient. If the latter two are perfectly normal, the infection causes a "stepping-up" in the metabolism, as in an acute infectious disease. As the duration of the chronic infection injures the organism and its state of nutrition, the metabolism is put under the influence of mal-

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nutrition. Therefore, Grafe takes the position that there is a need for large amounts of carbohydrates in the diet of tuberculosis patients, especially in the early stages.

Carbohydrates play a very important rôle in diseased and in normal persons. They are the greatest sources of energy, are necessary for the complete oxidation of fats, and are protein sparers. Ingested carbohydrate foodstuffs eventually reach the blood-stream chiefly as dextrose. The general theme of carbohydrate metabolism concerns itself with the storage of dextrose in the liver and heart as glycogen, and then the timely conversion of glycogen back into dextrose with the maintenance of a normal blood-sugar level.

Some men restrict carbohydrates, believing that the liver is functionally weak in active cases of pulmonary tuberculosis. Rabuchin carried out numerous studies of alimentary hyperglycaemia and of the glycaemic curves after the administration of adrenalin. He concluded that there was, in pulmonary tuberculosis, a disturbance of sugar-formation and sugar-oxidation due to dysfunction of the liver and the adrenalin system.

We now know that this hepatic dysfunction occurs only in some advanced cases. The curable cases have normal hepatic function. Others believe that the protective action of diets high in carbohydrates is based on the presence of an abundance of glycogen in the liver.

At the Tuberculosis Division of the Cook County Hospital in Chicago approximately 1,300 patients are seen yearly. For the most part these have advanced types of tuberculosis. With a capacity of some 400 beds, we felt that we had ample clinical material and facilities to study the effect of increased carbohydrates in the diet on the tuberculous process.

With the exception of complicated and diabetic patients, the average minimum diet consists of about 1,600 calories (carbohydrates 218 gm., protein 70 gm., fat 54 gm.). This diet is rich in carbohydrates and low in fats. Friends and relatives are permitted to bring in food and delicacies from the outside, but these are not weighed or measured, so that an accurate diet cannot be ascertained. With a minimal caloric intake of 1,600 calories, we felt that from a nutritive point of view we could push up the total to about 2,400 calories by adding 800 calories in terms of sugar. Thus, we could study the effect of the added carbohydrates on the nutrition, the clinical condition of the patient as indi-

cated by the weight, pulse, respiration and temperature, and on the blood-sugar.

Thirty-five patients were selected, 16 men and 19 women, of various types. Studying the previous weight-charts, we selected cases in which the patients were gaining in weight, losing in weight, and maintaining a stationary level. For our controls we used weight-curves of these same patients prior to the experiment and after it was concluded.

We elected to use Karo syrup and Dyno sugar for this experiment, for the reason that Karo syrup is substantially a mixture of dextrin, maltose and dextrose in a nonirritating and easily digestible form, while Dyno is pure dextrose, also nonirritating and easily digestible.

For a month we fed the extra carbohydrates to these 35 patients, dividing the 800 calories between two meals in the form of desserts and drinks. A special dietitian and cook prepared the sugars in a palatable, tasty and pleasing manner. The whole essence of the culinary art was used to prepare these foods so as to appeal to the patients. Eleven patients were fed the combined Karo syrup and Dyno sugar; twelve received only Dyno sugar and twelve only Karo syrup.

The weights of the patients were checked at weekly intervals, and the T.-P.-R. was recorded daily. The reactions and appetites of the patients were noted. Blood-sugar determinations, using the Benedict, Folin-Wu modification, were carried out before and after the experiment. The urines were repeatedly checked for sugars.

Summary: The weights of these 35 patients were recorded, and the results for the month preceding, during and after the experiment were charted in terms of loss(−) or gain(+) or no change(0). The results follow:

1: Nine patients were gaining before the experiment began. Of these, eight showed a greater increment of weight increase,—from 1.75 to 6.0 lbs. One showed no change.

2: Twenty-three patients were losing weight before the experiment began. Of these, sixteen showed a gain in weight of from 0.5 to 3.0 lbs. Four stopped losing weight and two lost less than previously. One showed no change.

3: Three patients gained nothing before the experiment began. During the experiment all three gained from 2.0 to 5.75 lbs.

4: Twenty-six patients lost weight in the month after the experiment (0.5 to 3.0 lbs.), six continued to gain (0.5 to 1.5 lbs.), two went home, and one did not lose or gain.

TABLE 1

NUMBER	SEX	AGE	TYPE	SPUTUM	GLYCOSURIA	BLOOD-SUGAR		SUGAR USED	WEIGHTS AT MONTHLY INTERVALS			WEIGHT (GAIN OR LOSS)
						Before	After		Before	During	After	
						mgm.	*mgm.*					
1	F	20	MAB: pleurisy with effusion	Negative	Negative	97	99	K & D	−2.0	+3.0	+0.5	+
2	F	14	FAB	Positive	Negative	86	88	K & D	+2.25	+2.25	−0.5	0
3	F	23	FAB	Positive	Negative	85	97	K & D	−2.0	0	−2.5	+
4	F	40	FAB: with right cavity	Positive	Negative	126	98	K & D	+0.5	+3.25	−1.0	+
5	F	26	FAB	Positive	Negative	96	81	K & D	+0.5	+2.25	−2.0	+
6	F	22	FAB—MAB	Negative	Negative	98	75	K & D	−0.5	+1.5	−1.0	+
7	F	15	FAB: with right cavity; toxic	Positive	Negative	95	81	K	−2.5	−1.0	0	+
8	F	58	FAB	Positive	Negative	98	99	K	−3.5	+2.5	−2.0	+
9	F	38	MAB	Negative	Negative	83	85	K	−3.25	+2.25	−1.0	+
10	F	18	MAB	Positive	Negative	83	87	K	−1.25	+2.5	−0.5	+
11	F	26	FAB	Negative	Negative	100	97	K	+0.5	+2.0	−0.25	+
12	F	26	FAB: with right cavity	Positive	Negative	95	82	K	−1.75	+0.5	−1.5	+
13	F	42	FAC	Positive	Negative	92	100	K	−1.0	+2.75	−2.25	+
14	F	45	MAB	Positive	Negative	97	99	D	0	+2.0	−3.0	+
15	F	44	FAB: with left cavity	Positive	Negative	94	102	D	−1.75	0	−1.5	+
16	F	24	FAB	Positive	Negative	100	98	D	+1.75	+2.75	−2.0	+
17	F	56	FAA	Negative	Negative	111	113	D	0	+5.75	−0.25	+
18	F	35	MAB	Negative	Negative	88	100	D	0	+4.0	−1.0	+
19	F	44	FAB: with right cavity	Positive	Negative	94	94	D	−0.5	+2.25	+0.25	+
20	M	21	MAB: pleurisy with effusion	Negative	Negative	103	100	K & D	+2.0	+6.0	−3.0	+
21	M	43	FAA	Positive	Negative	98	101	K & D	−0.5	+2.0	−1.0	+
22	M	32	MAA	Negative	Negative	94	100	K & D	−3.5	+1.5	+0.5	+
23	M	46	FAB: with right cavity; toxic	Positive	Negative	86	77	K & D	−0.5	−0.5	+1.5	0
24	M	40	MAA	Positive	Negative	108	105	K & D	−2.0	+2.0	−0.5	+
25	M	42	FAB	Positive	Negative	102	106	K	−1.5	+2.75	−0.75	+
26	M	72	FAB	Positive	Negative	112	108	K	−1.75	0	−1.75	+
27	M	49	FAB: with right cavity	Positive	Negative	86	92	K	−4.5	+1.75	+1.5	+
28	M	65	FAB	Positive	Negative	112	110	K	−3.75	+2.25	−1.0	+
29	M	18	FAB	Positive	Negative	118	120	K	−2.0	0	−1.0	+
30	M	15	MAB	Positive	Negative	98	101	D	+2.0	+6.25	−3.0	+
31	M	36	FAB: with right cavity	Positive	Negative	(Refused)		D	−2.5	−0.5	−2.0	+
32	M	46	FAB: with left cavity	Positive	Negative	112	110	D	−1.75	+3.0	−1.5	+
33	M	45	MAB: pleurisy with effusion	Negative	Negative	86	77	D	+3.5	+9.5	home	+
34	M	24	FAA	Negative	Negative	98	100	D	−2.0	+1.5	+0.5	+
35	M	40	FAB	Positive	Negative	98	91	D	+2.0	+7.5	home	+

No marked variations in the blood-sugar were noted. All urine examinations were repeatedly negative for sugar. No patients showed any evidences of gastrointestinal disturbances as the result of the extra sugars: rather, all looked forward to these desserts and drinks with relish, while a marked increase in the appetite of these patients was noted.

Thirty-three of the thirty-five patients benefited by the extra carbohydrates, as indicated by the weight and the clinical course.

DISCUSSION

Much study has been done on carbohydrate metabolism in tuberculosis. As far back as 1913 it was believed that diabetes predisposed to tuberculosis. It was observed that in a number of cases there was a marked improvement in the diabetic-metabolic disturbance as the tuberculous process progressed. Severe acidosis was very rare and glycosuria was diminished. Under insulin treatment there occurred hypoglycaemic symptoms difficult to interpret in view of the earlier tolerance and general condition. This increased insulin susceptibility or, in other words, the increased tolerance to carbohydrates in a febrile patient was striking. Lundberg, who first made these observations, concluded that a cellular process like the tuberculous process excreted an insulin-like substance into the blood. This explained the disappearance of the glycosuria and the marked susceptibility of the patient to insulin. He made extracts of the tuberculous glands and lungs of freshly killed cattle, and these were injected into white mice. A typical insulin reaction characterized by convulsions and collapse occurred and was remedied by the injections of dextrose. Extracts made of normal tissue, tubercle bacilli and tuberculin did not exert this affect. This insulin-like substance was called "para-insulin." Lundberg therefore concluded that the presence of tuberculous granulation tissue in the organism caused disturbances in carbohydrate metabolism similar to those caused by insulin. The symptoms of weakness, perspiration, hunger, pallor, tachycardia, and lowered blood-pressure were expressions of an extra-pancreatic formation of insulin by the tuberculous tissues.

Sendon studied the problem of carbohydrate metabolism in tuberculosis from another point of view. He found an increase of lactic acid in the blood of tuberculosis patients. Therefore, he believed that the trouble was due chiefly to a disturbance of Meyerhof's cycle, that is, the transformation of carbohydrates into lactic acid and then the

re-conversion of the lactic acid into carbohydrates. The first step occurred readily as it was an anaerobic process, but the conversion, in the presence of an oxygen deficiency because of the tuberculous process, could not take place. This work, however, has not been confirmed.

Many men have studied carbohydrate metabolism extensively from the viewpoint of glucose tolerance. Shimizu studied the blood-sugars of 118 patients with various types of pulmonary tuberculosis. He found that these varied from 0.062 to 0.135 per cent, the average being 0.09 per cent. In 38 normal cases it varied from 0.067 to 0.112 per cent, with an average of 0.088 per cent. In mild cases the average lay near the normal mean, while in severe cases the readings varied greatly. In very active cases with great toxicity there was a tendency to hyperglycaemia, especially in cases with haemoptysis or involvement of the meninges.

Kramer studied the curves of the blood-sugar in 100 tuberculosis patients. He concluded that such patients have a higher tolerance for sugars.

Nakajo made a study of alimentary hyperglycaemia. He found that patients with mild forms and patients with advanced but static types of pulmonary tuberculosis had normal curves. Patients with progressive, advanced forms of tuberculosis showed that the blood-sugar content increased rapidly after the oral administration of sugars, but that the content quickly decreased to its original values.

Shimizu carried out a similar study and confirmed Nakajo's work. He concluded that, if tuberculosis patients were fed to overweight without reference to the disturbance of sugar regulation, a true diabetes might develop, especially in patients of good nutrition in whom the glycaemic curves were high and returned slowly to normal.

In our work we found no marked changes in the blood-sugar. No glycosuria was noted in any of these patients.

CONCLUSIONS

In studying a series of 35 patients, the regular diet of 1,600 calories was increased by 800 calories in terms of Karo syrup and Dyno sugar (dextrose). Thirty-three of these 35 patients were definitely benefited by this procedure. Those patients, who had been gaining in weight before the experiment began, had a greater increment of weight increase during the experiment; patients, who had been losing weight before the

experiment, began to gain in weight, stopped losing, or lost less than previously; those, who maintained a stationary level before the experiment began, gained weight during the experiment. Two of the 35 patients showed no change. Twenty-six of these patients lost weight in the month after the experiment, whereas 6 patients continued to gain; two went home, and one did not lose or gain.

All the patients showed a high tolerance for the Karo syrup and the Dyno without any evidences of gastrointestinal upsets. No glycosuria was present in any of these patients. The blood-sugar was within normal ranges before and after the experiment. Karo syrup or Dyno, used alone or in combination, showed no difference in results obtained.

We feel that the extra carbohydrates were beneficial to the patients and form a necessary part of the dietary treatment of pulmonary tuberculosis.

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THE EVOLUTION OF PULMONARY TUBERCULOSIS[1]

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In tracing the evolution of this very variable disease it will be our aim to correlate the more important of the numerous additions to our knowledge which have come to us through the truly enormous amount of laboratory and clinical study which has been made in recent years, and at the same time to attempt to simplify our thinking concerning tuberculosis out of the confusing mass of material which is available.

Toward this end it is proposed to set up a simple basic underlying pattern for the evolution of the disease, upon which we will endeavor to trace its numerous variations in terms of certain definite underlying principles.

THE BASIC PATTERN

This pattern is composed of three basic phases of the disease.

1: The Primary Infection: This takes place from outside sources, usually human, and is generally localized in the lung, less frequently in the intestinal tract.

The initial primary lesion is in the lung but is regularly followed by a secondary involvement of the regional lymph nodes at the root of the lung. The primary lesion thus has two components, one pulmonary and the other lymphatic. Together they constitute what is known as the *Primary Complex*, whose two components are designated the *pulmonary* and the *lymphatic pole* of the primary complex, respectively.

2: Generalization of the Infection: In the evolution of tuberculosis in the body the infection may not remain localized in the Primary Complex but may be disseminated into other parts of the body through the lymph- or blood-stream. Such dissemination usually originates from the lymphatic pole.

3: Localization of this Secondary Infection: The bacilli thus dissemi-

[1]From the Tuberculosis Service of Bellevue Hospital, New York City. Presented at a Symposium on the topic, *Respiratory Diseases*, at the Postgraduate Fortnight of the New York Academy of Medicine, October 28, 1935.

nated from the primary complex may reach any organ, but invariably reach the lungs where they are caught and localized, causing secondary lesions which in some cases we will designate as *Transitional Forms*, or, more commonly, a definite type of disease which is termed *Phthisis*.

Phthisis may also arise when no dissemination from the primary complex occurs, from secondary reinfection from the outside by inhalation.

These three forms, the Primary Complex, the Generalizing Forms and the Localized Forms, constitute our basic pattern of the disease.

REINFECTION

Pulmonary tuberculosis as recognized clinically, with the exception of the rare *acute primary complex*, is therefore a result of a reinfection in a body already primarily infected.

This reinfection may be either exogenous, a new infection from the outside by inhalation, or endogenous, a spread from the primary complex through the lymph- or blood-stream. The relative incidence of these two methods of reinfection is important from the standpoint of pathogenesis and epidemiology.

Inasmuch as the lesions resulting from the primary infection are, as a rule, not serious, the prevention of damaging tuberculosis depends upon the control of reinfection. If, then, this danger of reinfection is mainly from the outside, its prevention depends upon the avoidance of contact with cases of open tuberculosis, and the primary lesion is of little or no consequence. If, on the other hand, the danger of reinfection lies in the lighting-up of quiescent primary lesions and the multiplication of tubercle bacilli from them through the lymph- or blood-stream, then the problem is the prevention of such mobilization, so that the behavior of the primary lesions becomes of the greatest consequence.

In this country in recent years our clinical thinking and prevention program have been largely based upon the first hypothesis, namely, the dominating importance of exogenous contact reinfection. Recent studies cast considerable doubt upon the correctness of this conception; and at the present time there exists, especially in Continental Europe, a school of thought which emphasizes the predominating importance of the second hypothesis, namely, the danger of pulmonary tuberculosis developing from the exacerbation of the preëxisting quiescent lesions. It is my personal belief that while contact exogenous pulmonary reinfection occurs frequently, there is evidence that the majority of cases of active pul-

monary tuberculosis result from previous foci and that there is need of a wider appreciation of this fact in this country.

RESISTANCE AND DOSAGE

Whether the reinfection occurs from either exogenous or endogenous sources, the character of the resulting lesions is very variable, depending upon many factors of which the cellular resistance of the body and the dosage of infection are predominantly important. If the dosage is small and the resistance high, no disease whatever may result; and, beyond this, all gradations of disease from very mild to extensive, progressively fatal lesions are possible.

Resistance to tubercle infection may be natural or acquired.

Natural resistance varies with age, race and family and individual constitution, but no human being is naturally entirely immune. The fact that in civilized communities a great majority overcome infection without the development of tuberculous disease is proof of the presence of widespread natural resistance.

Acquired resistance is the result of previous tuberculous infection, successfully localized. This changed reaction is known as allergy and is characterized and recognized by sensitivity to tuberculin. Allergy is not immunity but it so changes the reaction to reinfection that a larger dosage is necessary to produce disease and when produced it has a more definite tendency to remain localized. In allergic individuals the disease tends to be more chronic, and in the nonallergic the lack of resistance leads more readily to acute disseminated disease such as is encountered in the virgin soil of young children and in primitive races.

When present, this immunobiological reaction, allergy, varies greatly in different individuals and in the same individual at different times, and there is some evidence in favor of the contention that it may vary in different organs of the same individual at the same time, particularly in the lungs. It is, of course, affected by the character and extent of the primary lesions but it is also influenced by other intercurrent factors such as other diseases (measles, whooping cough), general nutrition and undue physical or emotional strain. It is probably these latter factors which explain the greater prevalence of tuberculosis among the poor.

The factor of quantity or *dosage* of tubercle bacilli has also a marked influence upon the lesions resulting from reinfection. But the presence of large dosage available for reinfection depends upon the multiplication of bacilli in the body and this in turn depends upon the resistance.

It has already been noted that with very small dosage no lesions whatever may result and that all gradations of disease may be produced by variations in the dosage, modified by the effect of varying resistance. This applies equally to exogenous and endogenous reinfection. The effect of variation in the virulence of the bacilli is slight as compared with dosage.

The primary lesion, due usually to inhalation of bacilli, is produced as a rule by a minimal dose. Under ordinary circumstances the conditions operating in reinfection by inhalation, limit the possibilities also to minimal dosage. It is for this reason and also taking into account the increased resistance present after the primary infection that we believe that it is less easy and less likely that reinfection lesions in the lungs are produced by exogenous inhalation than by endogenous reinfection from preëxisting lesions. It seems probable that exogenous inhalation reinfection requires for its production prolonged or intimate contact with sources of considerable amount of infection. Such conditions of course exist in the homes of many cases of active open pulmonary tuberculosis, but with the progress of modern sanitation, particularly by institutional segregation, they are becoming progressively less, and with the danger well known and the remedy available the prevention of such reinfection is definitely possible and in some communities is already in sight.

The possibilities for mobilization of bacilli from the primary lesions through the lymph- and blood-stream are numerous and variable. Mobilization may never occur, or it may occur at intervals in very small dosage producing either no lesions or very mild inconsequential ones, or, on the other hand, the discharge of bacilli from the lymphatic component of the primary complex may be enormous and overwhelming, producing generalized miliary tuberculosis.

Between these two extremes we see the intermittent discharge of bacilli in moderate numbers which may find lodgment in any organ of the body but, on account of the lungs' anatomical situation, bacilli practically always reach and lodge in the lungs where we most commonly find the resulting secondary lesions. The character and extent of these lesions will depend upon the dosage and the momentary resistance of the body present at the time of such reinfection.

The determining factors favoring such discharge are in the main mechanical and to a considerable extent accidental and unavoidable, but also to a considerable degree they depend upon physical strain and intercurrent disease, and to that extent may be preventable. The essential

fact to be emphasized is that every primary lesion, however latent and apparently innocuous, is a potential source of reinfection, that the early appearance of such lesions will only be recognized if such cases are under regular supervision, and that the danger of intercurrent disease or of unusual strain should be recognized and offset as far as possible by special care in the prevention of intercurrent diseases, or during convalescence from them, and by the avoidance of strains or by a special building-up program if they have occurred. What may be termed a protective environment of rest and building-up of general bodily health is the best, though still limited, program of prevention of such endogenous reinfection.

After secondary lesions are produced in any organ either by the exogenous or the endogenous method, then the secondary lesions become also potential foci for the further spread of the disease. Such spread is of course endogenous, but it is no longer likely that it will occur by the general lymph- and blood-stream, although this does occasionally take place at this stage; it is by direct extension to neighboring tissue or particularly through the natural anatomical tracts of the body that the bacilli travel from the secondary lesions to new areas. This method of extension is designated *intracanalicular spread* and in the case of the lungs it is called *bronchogenic spread*. Through the bronchi the bacilli may of course reach any or all parts of the lungs but the spread is most apt to be from above downward, either to the same or opposite lung from the infecting focus. Through the trachea the infected sputum may involve the larynx and then may be swallowed, and thus the alimentary canal may become involved, most usually in the iliocaecal region. The same method of intracanalicular spread occurs in the genitourinary tract in the case of tuberculosis of any of those organs.

In this method of spread, dosage of bacilli and tissue resistance to them also play an important part in determining the extent and character of the resulting new lesions. Dosage undoubtedly plays the leading rôle here.

In the case of the lungs, with which we are primarily concerned, the opportunity for heavy and extensive bronchogenic infection occurs when there is a large amount of heavily infected sputum, as in the presence of caseation and cavity-formation or in the case of pulmonary haemorrhage, when the large amount of fluid blood may carry bacilli very easily and extensively to other parts of the lungs. It is to prevent this occurrence that treatment by artificial pneumothorax is especially valuable by clos-

ing cavities, diminishing the amount of sputum and controlling the liability to and the amount of haemorrhage.

Again, any of these new or tertiary lesions are potential foci for further spread in the same way as occurs from the secondary lesions, and again dosage and tissue resistance are the determining factors, especially dosage.

From these considerations it is obvious that the true conception of tuberculosis is not that of a static disease but rather of a potentially dynamic moving clinical picture, the nature of which depends upon very numerous factors and conditions, and which assumes various forms in such kaleidoscopic variety that it is only by a realization of the basic pattern of its evolution that any true understanding of it is possible.

We are now in a position to study in more detail the behavior of tuberculous lesions in the body in each of the three phases of the basic pattern, namely, (1) *the Primary Complex*, (2) *the Generalization Forms*, and, (3) *the Localized Organic Forms of Phthisis*.

1. THE PRIMARY INFECTION AND COMPLEX

The primary infection of the body by tubercle bacilli is always exogenous, and is usually by inhalation localizing in the lungs, more rarely by ingestion localizing in the intestines. The dosage is usually minimal.

A large percentage of human beings under ordinary conditions of life become so infected before reaching adult life; none is really immune, but the dosage being small the degree of natural resistance, which is very variable, plays the important rôle in determining the extent and character of the primary lesions.

Lodging first in the lung parenchyma, most frequently in the lower or middle zone near the periphery, a lesion is set up there and the bacilli are carried by the lymphatics to the regional lymph nodes near the hilum where other lesions are produced. As mentioned above, these two sets of lesions, one in the parenchyma and the other in tracheobronchial lymph nodes, constitute what is known as the *primary complex*.

The primary infection usually occurs without symptoms or signs, though, less frequently, it may produce an acute and extensive inflammatory reaction with accompanying symptoms of fever. In both instances the reaction, whether slight or extensive, tends to subside and localize in the two poles of the primary complex, but the subsequent behavior is very variable.

Behavior of the Primary Infection

1: Usually the infection remains latent and localized, the lesions becoming largely calcified and producing no further symptoms during life, but they can uniformly be recognized by the roentgenogram.

2: The lesions localized in the primary complex may exacerbate locally. Such exacerbations may be slight and confined to neighboring tissues of either pole, which are infected through local lymphatic or bronchogenic spread; or the exacerbation may be severe, in which case it is uniformly from the lymphatic pole and usually by eruption of a considerable number of bacilli from the caseating node into a bronchus and thus infecting the lung. Severe caseating tuberculous bronchopneumonia may thus result.

In general, however, these local exacerbations tend to calcify readily and to become localized again.

3: Both the lymphatic pole of the primary complex and the lesions resulting from its localized exacerbation are liable at any time to discharge bacilli in varying amounts into the general lymphatic and bloodstream of the body and so produce lesions in any part of the body, especially the lungs. The route of such infection is usually from the tracheobronchial nodes upward through the large lymph channels and so into the vena cava at the venous angle, and thus distributes the bacilli through the general circulation.

It is important to recognize the fact that *all* such primary lesions are potentially a source of such systemic infection and that it is difficult or impossible to prognosticate which will remain safely latent and which may disseminate and cause serious disease.

2. THE LESIONS CAUSED BY GENERALIZATION OF THE INFECTION

Lymphohaematogenous Forms of Tuberculosis

We have already described, and it is of course obvious, how such bloodstream dissemination may reach any organ of the body but it is in the lungs that the bacilli are most apt to lodge because of the net or screen-like structure of those organs and their anatomical situation, which requires that all the blood of the body must eventually pass through them, thus explaining the predominating incidence of pulmonary tuberculosis as compared with all other organs.

These endogenous and haematogenous lesions in the lungs have certain definite characteristics which it is important to recognize from the stand-

point of prognosis and treatment, as well as for the understanding of the pathogenesis of the disease. These Lymphohaematogenous Forms of Pulmonary Tuberculosis may be separated into several categories.

1: Acute Miliary Tuberculosis of the Lungs: The lung lesions here are usually a part of a generalized miliary tuberculosis throughout the body. This is produced by a one-time eruption of tubercle bacilli into the blood-stream in massive doses and the lesions are disseminated in myriad number and are of fine and uniform size (millet seed).

2: Protracted Disseminated Tuberculosis of the Lungs: This is also a part of a generalized dissemination. The lesions here are the result of repeated blood-stream dissemination, considerable in amount but less overwhelming than is the case in generalized miliary tuberculosis. The lesions are also disseminated throughout the body, are very variable in size and age, but in general are larger and more irregular than in miliary tuberculosis, with a tendency to localization, caseation and coalescence, so that the disease runs a more protracted and discontinuous course although uniformly fatal after several months. The lung and other visceral lesions are characteristically accompanied by marked involvement of the lymph nodes and the serous membranes. This form is most frequently found in this country among the Negro, West Indian and Mexican races.

3: Chronic Disseminated Haematogenous Pulmonary Tuberculosis: This form is represented clinically by a great variety of lesions which have been especially studied by the French School under the lead of Bard and Piéry, who elaborated a very complex descriptive classification of them. For my present purpose it is sufficient to attempt to identify the group as a whole, as the various forms included in it have certain characteristics in common.

The lesions are produced by the occasional moderate discharge of bacilli into the blood-stream. In the lungs these lesions are characteristically bilateral. They are more or less symmetrical, and tend to localize toward the periphery and in the upper lobes. They have a marked tendency to early calcification. As they are brought to the lung by the blood-stream, these bacilli lodge in the capillary network in the stroma of the lung and there set up lesions in the form of tubercles. This localization in the interstitium is in contradistinction to the first lesions produced by exogenous inhalation infection which is characteristically an endobronchitis, that is, within the air-passages. This dif-

ference in localization largely explains the difference in their clinical course.

The most striking characteristic of this form is the paucity or even absence of symptoms and signs which they present in the majority of instances. They are very frequently to be recognized only by roentgen examination. As the lesions are very apt to be partly calcified, the roentgen picture is usually sharp and definite. In other cases the lesions are numerous fine granulations closely resembling those of miliary tuberculosis. Many of these cases go through life without recognizable symptoms, but the lung lesions may be reactivated in the same way, and under the same conditions, as any other tuberculous lesions already described.

In many cases, however, definite symptoms occur. An important group of cases are those in which pleurisy with effusion is the first manifestation of the reinfection. Such cases of so-called *idiopathic pleurisy* are very common. Their tuberculous nature is definitely established and their development from haematogenous dissemination is probable and quite generally admitted. The extent of the exudate, out of all proportion to the discrete pleural focus, is probably an expression of allergic hypersensitiveness during the generalization phase.

The most common group in this class are those which present varied, protracted but intermittent symptoms and especially those which are general or systemic, as opposed to local symptoms directly referable to the lung. Here are found many of the cases of mild protracted fever, those characterized by malaise and fatigability or nervous instability, and those with symptoms of chronic indigestion, all of which are usually associated with loss of weight and strength. Cough and expectoration are usually slight or absent. Haemoptysis occurs only when the lesion opens into the air-passages, as is apt to occur in the calcified lesions, often repeated slight haemoptyses occurring without other symptoms whatever.

The symptoms of such mild haematogenous forms respond most satisfactorily to proper treatment which is prolonged absolute rest, but relapse is frequent and easy, and years of supervision and careful living are necessary to ensure against such relapse and the possible progression of the dissemination.

These haematogenous lung lesions do not always remain confined to the interstitial parenchyma. Their anatomical proximity to the air-passages renders extension of the process into these passages very easy

and frequent when caseation or reactivation of these foci occurs. The subsequent development of the disease and its symptomatology is similar to that of the exogenous inhalation forms, with the extension of infection by bronchogenic spread with the development of focal lung symptoms such as cough, expectoration, haemoptysis; and the process then goes on into the phthisical forms and gradually assumes the same characteristics as those processes arising from exogenous infection, so that in these end-phases identification of the method of reinfection is impossible.

3. TRANSITIONAL FORMS OF PULMONARY TUBERCULOSIS

These forms are of haematogenous origin but are composed of larger lesions than those described under haematogenous forms. Like these, they are bilateral and are situated in the upper lobes, but because of their extent they are more likely to exacerbate, in which case they extend very slowly by proliferation, coalescence and gradual caseation, with many periods of quiescence or very low-grade activity alternating with those of exacerbation. Ultimately, as these lesions progress they break through into the air-passages, when the bronchogenic element comes to prevail in their progression and gradually they go on and into the form of chronic pulmonary phthisis.

Occupying for often long periods of time an intermediate position between the usual haematogenous forms and the frank phthisical forms, they deserve a separate description in the slow evolution of the disease: hence our designation of them as *Transitional Forms*.

4. CHRONIC PULMONARY PHTHISIS

This is the usual form encountered clinically in adult chronic pulmonary tuberculosis. It may result from either exogenous or endogenous reinfection.

We have already traced its evolution from the haematogenous forms. In the exogenous form active disease is most apt to manifest itself more or less acutely in the upper lobe of one lung, in the subapical region. This method of onset has been designated *Infraclavicular Infiltration*, and is characterized by a grippe-like syndrome of symptoms which frequently subside in two or three weeks, creating a false sense of security if the true condition is not recognized. Some of these infiltrations will resolve to a remarkable degree, but, unless treated promptly and properly by prolonged rest, they soon exacerbate, caseate and go on into progressive

phthisis. Whether such infiltrations are always of exogenous origin or may be due to the exacerbation of previous haematogenous lesions, and whether they always start subapically or may develop as an exacerbation of a previous apical lesion, are much debated points still not entirely and categorically determined.

After the stage of phthisis is established through whatever process, then the future course of the disease, though variable, follows a definite pattern quite different from the evolution of the haematogenous forms.

The lesions may remain localized, in which case reparative processes of resolution, fibrosis and calcification may occur; and, with proper treatment, arrest of the progress of the disease may result.

Under ordinary circumstances, however, the natural tendency of the disease is to progress; and this occurs, as already explained, by extension through the air-passages, that is, by bronchogenic spread. Very exceptionally the blood-stream may be invaded even in this stage and general miliary tuberculosis may thus result. The early lesions of frank phthisis are a caseating endobronchitis but tend to develop into a localized caseating bronchopneumonia. From this point the bacillus-laden sputum carries the infection to other portions of the lungs in a craniocaudal direction or by intrabronchial spilling across into any portion of the opposite lung. The character and extent of these secondary lesions depend largely upon the dosage of the intrabronchial infection, and to a far less extent upon the amount of tissue resistance which it encounters. They may vary all the way from very severe foci of new disease, usually in the neighborhood of the present lesion, to all forms of tuberculous infiltrations, focal or confluent, bronchopneumonic or caseous pneumonic processes of an entire lobe. These lesions in turn become potential foci for further bronchogenic spread in the same manner as the previous lesions.

The occurrence of haemorrhage affords the opportunity for extensive bronchogenic spread of the infection, the nature of the resulting lesions again depending upon the dosage of infection. In some cases of haemorrhage the fluidity of the blood may separate the bacilli into very small units, which, when spilled extensively, set up small, miliary-like tubercles closely resembling haematogenous miliary dissemination. This result is termed *Bronchogenic Miliary Pulmonary Tuberculosis.*

Outside of the occurrence of haemorrhage the chief danger of serious and extensive bronchogenic spilling is from caseating lesions secreting sputum heavily laden with bacilli. It is for this reason that open cavities

producing large quantities of sputum constitute such a serious menace of progression of the disease.

The modern methods of treatment by collapse, artificial pneumothorax or more radical surgical procedures, thoracoplasty and the like, are particularly valuable in controlling the danger of bronchogenic spread both from haemorrhage and from open cavities.

Further extension of the disease outside of the lung is possible through the intracanalicular method of spread. Especially the infected sputum may reach the larynx through the trachea and cause tuberculous laryngitis, or it may be swallowed and cause intestinal tuberculosis, usually in the iliocaecal region.

In the evolution of the phthisical process not only may progression of the disease occur, but also there are usually longer or shorter periods of quiescence with abeyance of the active progress of the disease and the subsidence of the symptoms, so that the usual course is not one of uninterrupted progression or retrogression but a series of intermittent periods of exacerbation and of quiescence or improvement.

At any period in the evolution of the process, reparative processes of resolution, fibrosis and calcification may occur to a greater or less extent. The resistance of the individual and the character of treatment are the dominating influences in this direction.

It is the object of all treatment to reinforce these natural reparative processes; and this constitutes the rationale of the hygienic-dietetic regimen in which strict rest is the most important factor, and the results obtained by this method have been greatly enhanced in recent years by the brilliantly successful result of collapse therapy, as has already been indicated. The numerous specific methods of treatment which have been suggested from time to time are in the main directed also toward increasing the natural reparative processes. Up to the present time none of them has proven efficacious.

PRACTICAL APPLICATION

This concludes our consideration of the more important clinical manifestations of the underlying principles which occur in the evolution of pulmonary tuberculosis.

It may be helpful to summarize the application of this knowledge lest it might be considered to be of more theoretical than practical interest to the general practitioner of medicine.

1. Classification of Pulmonary Tuberculosis

Many systems of classification of pulmonary tuberculosis have been proposed. In this country the system devised by the American Sanatorium Association and endorsed by the National Tuberculosis Association is in general use. This consists of a division of the disease into three stages, depending upon the extent of the disease modified by the additional consideration of the constitutional symptoms. In addition, the effect of treatment upon the course of the disease is indicated by the terms of *Apparent Cure, Arrest* or *Apparent Rest, Quiescent* and *Progressive.*

This system has proved very valuable for statistical purposes and for the study of comparative results of treatment. It applies primarily to pulmonary phthisis and takes no cognizance of the differences between haematogenous and exogenous reinfection forms. Also, any stage system of classification is necessarily rigid and, unless skillfully employed, is apt to imply a static character of the disease in any individual case rather than the changing picture which we have seen to represent the usual evolution of the disease.

In addition to this regular classification the National Tuberculosis Association has endorsed the use of the terms *Childhood* and *Adult forms* of the disease and these terms are in general use in this country.

By childhood forms are meant the lesions of the primary complex and some of the postprimary pulmonary lesions resulting from lymphohaematogenous dissemination. As recognized clinically the majority of these lesions are calcified. In the adult forms are included the various manifestations of pulmonary phthisis, and in this country these lesions have been assumed to be due predominantly to exogenous reinfection.

We believe the evidence to be conclusive that these childhood forms are quite as frequently to be recognized among adults as among children and that, while the primary infection is apt to occur during the early years of life, it can and often does occur in adults. Also, the evidence of the primary infection is often first recognized at the adult age even when it occurs in childhood, and, moreover, such lesions are potential sources of reinfection at any age, very frequently exacerbating into active disease only in the adult years under the stress and strain of life. In addition to these considerations, pulmonary phthisis of the so-called adult form occurs very frequently in children, although of course not so frequently as in adults, and the implied assumption that adult phthisis is most

regularly due to exogenous reinfection we believe to be definitely contrary to the evidence.

For all of these reasons we believe that a better understanding of the true picture of the pathogenesis of tuberculosis would be served if the designation of *Childhood* and *Adult Forms* were dropped from our nomenclature. In my own experience we have found the use of the terms *Primary Complex, Lymphohaematogenous Forms, Transitional Forms* and *Phthisical Forms* very helpful as a supplement to the use of the nomenclature of the National Tuberculosis Association.

2. Epidemiology and Prevention

A correct appreciation of the method of evolution has a very distinct bearing upon the epidemiology and consequently the prevention of pulmonary tuberculosis.

If the primary infection is under ordinary circumstances innocuous and the reinfection which causes serious pulmonary disease is in the main exogenous, then the problem of the spread of tuberculosis and its prevention can be safely centered in the prevention of such exogenous reinfection from contact with open cases. We are all familiar with the progress that has been made in this direction throughout the civilized world.

But if, on the other hand, our conception of the evolution of the disease be correct, then there is an equal or even greater danger of the reinfection occurring from endogenous sources through exacerbation and dissemination of infection from the apparently harmless primary lesions. The prevention of serious pulmonary tuberculosis from these sources consists in the appreciation of their potential danger and a suitable program of supervision and protection along the lines already indicated. This is also a part of our preventive program, but has by no means as yet been sufficiently developed.

There remains still another aspect of this problem concerning which there is as yet no agreement because we still lack sufficient knowledge of it. I refer to the question as to whether our ultimate goal should be the general elimination of all primary infection, that is, the practical extermination of all tuberculosis. Aside from the fact that at present such a goal is a Utopian dream, we are met with the evidence that in such uninvaded virgin soil the accidental occasional infection which must be expected would then be more apt to assume the character of acutely virulent disease which has already been frequently seen in certain primitive races and which might even take on the proportions of an extensive

acute epidemic. In addition to this, we are met with the argument that small primary infection produces allergy which in turn promotes, while not immunity, at least a certain amount of added tissue resistance to reinfection.

The present state of our knowledge would lead us to emphasize the factor of dosage as of the greatest importance in determining the seriousness of the reinfection both in allergic and nonallergic individuals and also whether the source of the reinfection be exogenous or endogenous. But this factor of dosage, as we have already indicated, is dependent upon variation in resistance which determines the degree of multiplication of bacilli in the body. At the present time our knowledge of the methods to be employed in the prevention of massive reinfection from exogenous sources is more precise and effective than is the case in dealing with the more latent and intangible endogenous sources.

3. Diagnosis

This is not the place to deal exhaustively with the subject of early diagnosis, but it is evident that a proper appreciation of the usual method of evolution of the disease must lead to its better and earlier recognition.

For example, the knowledge that primary or postprimary latent lesions are apt to exacerbate into active disease leads to an immediate suspicion as to the character of symptoms suggestive of tuberculosis only, if the presence of such primary lesions is known. The appreciation of the fact that almost all extrapulmonary tuberculosis is due to a systemic haematogenous infection and that such infection must also reach the lungs, would lead the physician or surgeon called upon to treat localized tuberculosis of the bones, joints, ischiorectal fossa or kidney, immediately and searchingly to investigate the lungs, where often lesions may also be found, although frequently giving no symptoms. Or, once more, the physician will appreciate the importance of the knowledge that the frequent mode of manifestation of pulmonary tuberculosis is by acute infiltration clearly simulating grippe, and that these symptoms usually quickly subside only to reappear later with more serious exacerbation of the disease, or that many forms of pulmonary tuberculosis, especially the haematogenous forms, give few or no physical signs so that roentgenograms are essential for diagnosis and in general are more reliable than the most searching physical examination.

Or, on the other hand, there will also grow the appreciation of the fact that very many roentgenographic shadows typical of tuberculosis do not

mean active disease but frequently represent quiescent residues requiring supervision and watching but no active treatment. This last point is to be particularly emphasized in these days of group examinations of apparently well people. Many a person has suffered the injustice of faulty though honest interpretation of such roentgenograms.

4. Prognosis

It is important to recognize the fact that haematogenous lung lesions are milder and are more amenable to treatment than are the cases of phthisis and that it is in general not until a phthisical form develops that the great danger of serious progressive disease occurs; also that in phthisis it is the cases of open cavity or haemorrhage that are in the greatest danger of bronchogenic spread.

Moreover, a knowledge of the varied pathogenesis of tuberculosis will make anyone, even the most experienced man, more cautious in being dogmatic in the prognosis of the course and outcome of any particular case of this pleomorphic disease.

5. Treatment

Just as the physician who appreciates the underlying principles of the pathogenesis of pulmonary tuberculosis will not enforce months of bed-rest for a patient because he has an X-ray shadow of an obsolete lesion or a positive reaction to tuberculin, so he will on the other hand know that apparently quiescent or obsolete lesions are potentially quite otherwise and when discovered need systematic supervision. He will also know that prolonged rest is the best treatment of all forms and will not be deceived by the periods of subsidence of symptoms which are a part of the process in every case usually long before a real arrest of the lesion has occurred. He will also appreciate that the open cavities and haemorrhage cases are the most dangerous ones, needing more absolute and prolonged rest and calling in many instances, if not most, for the early institution of modern collapse methods of treatment in addition to rest, both to prevent bronchogenic spread and to facilitate healing.

In conclusion, therefore, it would appear to be evident that only the physician who is willing to take the pains to understand the evolution of tuberculosis and to follow the development of our modern knowledge in this field, is competent and qualified to satisfactorily diagnose, prevent or treat pulmonary tuberculosis.

THE FIRST-INFECTION TYPE OF TUBERCULOSIS

Its Preallergic and Postallergic Stages of Development [1, 2, 3]

J. ARTHUR MYERS

In recent years, very careful microscopic studies have been made of the evolution of tuberculosis in the animal body. Vorwald (1) found that, one hour after injecting rabbits intravenously with 0.1 mgm. of human tubercle bacilli per kg. body weight, there were numerous collections of cells in the small alveolar capillaries, in some cases sufficient to obstruct the lumen. These groups of cells consisted almost exclusively of polymorphonuclear leucocytes which had grouped themselves about collections of tubercle bacilli, and some of them had already phagocytosed tubercle bacilli. At the end of two hours, the obstruction of the capillaries was more marked, and an hour later there had been a definite increase in the bacilli-laden polymorphonuclears in the alveolar walls with greater thickening of the wall due to accumulation of exuded mononuclear cells. At four hours, there was an increase in the accumulation of mononuclears, and an occasional one had phagocytosed tubercle bacilli. At the end of six, eight and ten hours, the majority of the tubercle bacilli were seen within the polymorphonuclears, but the large mononuclears contained more tubercle bacilli than in previous stages. At eighteen hours, the mononuclears predominated slightly. Some of the alveolar spaces were completely obliterated by exudate cells. There was considerable evidence at this period of degeneration of the polymorphonuclear leucocytes containing tubercle bacilli, and a good many of these degenerating cells had been phagocytosed by the mononuclear cells. Tubercle bacilli appeared to be present in larger numbers than in the preceding stages. At twenty hours, there had been an increase in mononuclear cells and a decrease in polymorphonuclear leucocytes.

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[2] Prepared with the aid of a grant from the Medical Research Fund of the University of Minnesota.

[3] Presented as part of a Symposium at the Joint Session of the Mississippi Valley Sanatorium Association and Conference on Tuberculosis, Madison, Wisconsin, September 13, 1935.

Vorwald's basic findings, namely, (1) a practically immediate polymorphonuclear reaction to tubercle bacilli introduced intravenously into an animal and (2) a very early degeneration of phagocytosing leucocytes, confirmed Krause's well-known work, published in several papers in the series, *Studies on Tuberculous Infection*, between the years 1920 and 1927. Krause had done intravenous injections of tubercle bacilli in rabbits and subcutaneous injections (groin) in guinea pigs; and had studied not only the cellular and tissue reactions to tubercle bacilli, but also the step-by-step course and localization of tubercle bacilli, following the several modes of experimental (1) first infection and (2) reinfection, in the animal body (guinea pig and rabbit).

At the end of a day, some areas of great thickening of the alveolar walls and obliteration of the adjoining spaces were seen. These showed evidence of typical tubercle-formation. The cell predominating in the reaction at this time was the mononuclear which had played the largest part in engulfing the tubercle bacilli. At the end of one week, there was still a preponderance of mononuclear cells, some of which possessed the characteristics of epithelioid cells. At the end of a month, tubercles were macroscopic. Mononuclear exudate cells predominated, but a few polymorphonuclears were seen, as well as typical lymphocytes. Central caseation of tubercles was frequently observed, in which large numbers of tubercle bacilli were found free. Concentrated around the tubercle were lymphocytes and plasma cells. Thus, the first response to tubercle bacilli was made by polymorphonuclear leucocytes. These cells ingested the bacilli in the blood-stream. They then accumulated in the capillaries, and this was the beginning of the focalization of tubercle bacilli. Around these focalized accumulations of polymorphonuclear leucocytes, large numbers of mononuclear exudate cells collected. They surrounded and phagocytosed bacilli-laden polymorphonuclear leucocytes, and then became the epithelioid cells of tubercle-formation. This focalization and walling-off of bacteria before sensitization appears may be an important factor in making primary tuberculosis a benign disease.

Many experimental workers have introduced tubercle bacilli of low virulence into the bodies of animals and have found that, following the growth of these microörganisms, the tissues of the animal's body became sensitive to tuberculoprotein. However, this seems to vary a great deal with the species, as shown by Vorwald (2) and others. In those species in which the tissues become sensitized a second dose of tubercle bacilli causes a sharp reaction, which is not seen following the first dose. For

example, if one introduces tubercle bacilli, in not too large amounts, into the skin of a normal guinea pig, almost no local hyperaemia is seen for several days; but, when even much smaller doses are injected into the skin of a guinea pig with specifically sensitized tissues, an intense and almost immediate (hours) local hyperaemia appears, due to vasodilatation. This is also true of other tissues in the animal's body; for example, when tubercle bacilli in small dosage are introduced into the peritoneal cavity of an animal that has never been tuberculous previously, one is unable to observe any significant immediate change, but the same dose of tubercle bacilli injected into the peritoneal cavity of a tuberculous guinea pig very quickly results in a pink color of the peritoneum and an outpouring of fluid into the peritoneal cavity. Long (3) has shown that small doses of tubercle bacilli and their products have no immediate effect upon the cells of the testes of normal guinea pigs. However, when equivalent doses of tubercle bacilli are injected into the testes of animals which have previously been sensitized, acute inflammation and degeneration of the cells begin almost immediately.

Some very interesting experiments have been performed on the effects of tuberculin on tissue cultures. For example, Stewart, Long and Bradley (4), and Holst (5), found that leucocytes from animals which had not been infected with tubercle bacilli were not harmed when they were brought in contact with tuberculin, whereas leucocytes from animals with tuberculosis were definitely damaged under the same treatment. Rich and Lewis (6) also exposed washed cells of normal and of allergic guinea pigs to measured amounts of tuberculin. They used hundreds of cultures of leucocytes and of spleen to demonstrate that the cells obtained from tuberculous animals are killed by amounts of tuberculin in which cells from normal animals grow freely.

Aronson (7) showed that "tuberculin from the human and from the bovine type of tubercle bacilli inhibits the growth of cells from explants of bone-marrow, spleen and testes of tuberculous guinea pigs, and is toxic for these cells, but has no effect on explants of the same tissues from non-tuberculous animals."

It is generally believed that the rat has a very high resistance to tuberculosis. However, Long (3) and Vorwald (2) have called attention to the fact that the albino rat is not completely resistant, although its disease does progress with extreme slowness. As determined by the usual methods, sensitiveness of the tissues in the rat is not well established through the development of tuberculous infection. In this con-

nection, Smith's (8) studies are very enlightening. He found that the normal albino rat will tolerate a dose of tuberculoprotein the equivalent of over 40 cc. of standard tuberculin per kg. body weight. However, an animal which has been infected with tubercle bacilli succumbs to an equivalent of approximately 10 cc. In a single dose Krause has injected a 400-gm. *nontuberculous* guinea pig *intravenously* with 35 cc. of water extract, a relatively pure tuberculin. The amount probably equalled the fluid content of the animal's blood-vessels. Yet, except for a rapidly passing unsteadiness and an almost immediate profuse serous diarrhoea, the guinea pig displayed no ill effects. (Personal communication.) If, according to Smith (8), one reduces the intake of vitamine A to a level which is just compatible with life, the infected rat will succumb to the equivalent of 1 cc. of standard tuberculin per kilogram of body weight. Therefore, although the rat's tissues do not appear to be sensitized when the tuberculin test is administered, Smith has shown that invasion by the tubercle bacillus results in an increased susceptibility of the rat to certain products derived from the bacillus, just as it does in the guinea pig. The difference is a matter of degree.

Seibert (9) states that she sensitized normal guinea pigs by weekly intracutaneous injections of 10 mgm. of tuberculoprotein of large molecular size. Subsequent studies of these animals showed that there existed a high degree of sensitiveness without any specific immunity or increased resistance to tubercle bacilli. On the contrary, as she says, "It seems to hasten and extend the lesion and to be associated with much more extensive necrosis and caseation than is found in unsensitized animals."

We have looked upon the first-infection type of tuberculosis in animals and man as that which begins its development in nonsensitized tissues, whereas the reinfection type starts to develop on tissues that have already become sensitive to tuberculoprotein. Therefore, it would appear that the animals which Seibert (9) sensitized and then infected with living tubercle bacilli immediately developed the destructive reinfection form of tuberculosis, whereas those which had not been sensitized developed the first-infection type of disease which was very benign but sensitized their tissues, after which any free tubercle bacilli set up the reinfection type of tuberculosis. This probably is what happens when an animal, such as the guinea pig, is inoculated in diagnostic work. The bacilli introduced cause practically no destruction of tissues at first; in fact, there is a period of ten days, more or less (depending upon "dosage"), before the tissues become sensitized, during which we cannot determine whether the animal

has been infected. After this period, however, destructive lesions begin to make their appearance, and the animal finally succumbs to tuberculosis of the reinfection type.

The studies of Lemon and Montgomery (10) with reference to the effects of sensitiveness of tissues on the development of destructive forms of tuberculosis are very significant. The conclusions of their extensive experimental work are as follows:

> When virulent organisms of Mycobacterium tuberculosis (bovis) are introduced into the pleural space of healthy rabbits, they constitute foreign bodies of the particulate type to which tissues react with a non-specific form of inflammation. The fluid and cellular parts of the resultant effusion are promptly resorbed, carrying with them the particulate material, which had been phagocytosed, and depositing it in regional lymph nodes and in remote organs. Many of the intracellular bacilli could not be removed, but remained within the lymph spaces or were included in cellular masses attached to the pleural surfaces. Up to this point, the reaction is entirely non-specific. Thereafter, the reaction becomes specific because the particulate matter is made up of living organisms and is capable of growth and division. Non-sensitive tissues are changed to sensitive tissues, and allergic reactions respond to reinfection as vast numbers of virulent bacilli are released into the tissues. The massive, persisting effusions are objective evidence of a specific response to reinfection.
>
> Tubercles develop on pleural surfaces as a result of persisting irritation of residual bacilli, and represent hyperplasia of histiocytes and regional fibroblasts. Epithelioid cells and giant cells appear as developmental changes in histiocytes. Similar tubercles develop in the parenchyma of the lung, in the regional nodes, and in remote organs wherever residual bacilli are harbored, and are increased in numbers by growth of organisms. Caseation and ulceration of tubercles into the lumen of bronchi and veins constitute hazards to the life of the animal by providing a means of rapid transport of organisms to uninfected tissues. The acute reactions and the lesions which bring about illness and death are final evidences of a specific reaction.

Apparently, the defense mechanism which attacks the tubercle bacilli, as described by Vorwald, differs very little from that which attacks even inanimate material of the particulate type, as shown by Lemon and Feldman (11), who introduced into the trachea of normal rabbits suspensions of particles of silica and, in another group in the same manner, suspensions of virulent tubercle bacilli of the avian type. They then killed these animals in pairs at equal intervals of from five hours to four weeks. The early cellular reactions which developed about the particles

of silica were essentially the same as those which appeared about the tubercle bacilli. In both cases, no significant differences could be discovered between the epithelioid cell of the tubercle and the mononuclear phagocyte of the silicotic nodule.

The tuberculous nodule retained its cellular integrity longer than the silicotic nodule; it developed a necrotic center more slowly and much more slowly became invested by collagen. The reticulum of the tuberculous nodule was slower in development and was composed of finer interlacing fibers. The tendency to the development of caseous, massive pneumonia and to a spread of ulceration into adjoining bronchi or blood vessels was much more evident in tuberculosis than in silicosis. The similarity of the structural unit or tubercle invoked experimentally in response to particles of silica and to bacilli of tuberculosis is so striking as to make their certain differential identification impossible by ordinary morphologic criteria.

Although the characteristics of the two processes were practically the same during the early period, definite differences were evident in the later stages. This was thought to be because of the inability of the silica particles to increase in number, while the tubercle bacilli remain alive, multiply, and thus set up progressive responses. Therefore, it is obvious that the growth of tubercle bacilli in the animal body or the introduction of a sufficient amount of their products of growth brings about a change in the tissues which results in a much more intense reaction to tubercle bacilli subsequently introduced.

There has been very little opportunity to study the effects of tubercle bacilli upon the human body before sensitization of the tissues develops. Indeed, a positive tuberculin reaction has been our first manifestation of the presence of tuberculosis in most cases studied. However, Ligner (12) has reported the case of an infant of seven months, whose tuberculin test was negative, while X-ray films of the chest revealed no abnormal findings on June 4. Two days later, June 6, he recovered tubercle bacilli from the gastric contents. On June 10, the tuberculin test was still negative, but on June 18 the test had become positive. Eight days later, June 26, evidences of infiltration made their appearance in the right lung.

Wallgren (13) has reported a group of children, whom he observed with negative tuberculin reactions but found the test positive with the onset of fever. As long as the test was negative, there was no elevation of temperature or other manifestation of disease. His patients had only the first-infection type of disease, and therefore their febrile reactions

were usually of short duration, after which the temperature again was normal, just as it was before the tuberculin test became positive.

Thus, in the human body, before sensitiveness of the tissues occurs, there are no outward manifestations of tuberculosis, but along with the appearance of sensitiveness there may be a brief febrile reaction which in some cases is soon followed by X-ray manifestations of a lesion in the lung.

Inasmuch as the tuberculin test has been our first diagnostic evidence of tuberculosis in the human body, and since it requires from three to seven weeks after infection before the tissues of the skin are sufficiently sensitized to give a positive reaction, the question arises as to whether it may be possible to detect evidence of the first-infection type of disease before the tuberculin test is positive. There are three possibilities: namely, differential leucocyte counts, the red-cell sedimentation test and examination for tubercle bacilli in the gastrointestinal contents and discharges. To determine whether the blood examination is of value would require a great deal of work on a group of individuals who had been carefully studied over a control period and were then exposed to open cases of tuberculosis. Inoculation is easily done in animals, but the question of comparable doses for human beings is important. We are not certain that the number of bacilli which set up the first-infection focus of tuberculosis, as we commonly see it in man, is sufficiently great to make enough demand on the neutrophiles to result in an appreciable increase in their number in the peripheral blood. This also applies to the monocytes and the lymphocytes later when they play the predominant rôle. We now have work in progress in an attempt to determine whether such changes can be detected.

The question also arises as to whether there is enough destruction of tissue to result in an acceleration of the red-cell sedimentation rate before sensitiveness appears. Wallgren (13) has observed a definite acceleration after the tissues have become sensitized and fever is present. To determine whether such changes occur before the tissues are sensitized would be of no particular practical value, inasmuch as the differential leucocyte counts and the sedimentation rate are not specific, and therefore one would almost be compelled to wait for the tuberculin test to become positive before arriving at a diagnosis. Moreover, no treatment except protection from further exposure is indicated in most cases of first-infection type of tuberculosis even after the tuberculin test has become positive.

We can follow some cases of the first-infection type of tuberculosis after the tissues become sensitized by periodic X-ray film examination and determine many facts about the evolution of this type. However, our evidence is indirect and can never be as satisfactory in some respects as that obtained by pathologists. We must keep in mind, however, that usually children or adults do not die of the first-infection type of tuberculosis; that it is only the occasional child who develops reinfection meningitis or miliary disease or who dies of some entirely different cause and comes to postmortem examination in whom the original primary focus in the pneumonic stage can actually be studied by the microscope. Therefore, when we begin with the earliest X-ray manifestations, we must bear in mind that sensitization is already present and continues throughout the course of the disease. We are of the opinion that the tubercle bacilli of first infection are so well focalized and surrounded by the defense mechanism of the body before sensitization appears that the subsequent development of the disease differs materially from that seen in those cases when foci begin to develop in tissues that have already been sensitized.

In the various animals studied, the same kinds of cells and tissues seem to have entered into the reactions to first contacts with tubercle bacilli. Yet, considerable variations in resistance to tubercle bacilli have been observed among the several species. It is therefore impossible to draw an accurate analogy between the occurrences in any one species and those in a human body, when first infected in each instance with tubercle bacilli. However, enough observations have been made by pathologists to lead us to believe that the early reactions are similar. The first defense is offered by the neutrophiles when they phagocytose the tubercle bacilli in the blood-stream. However, this defense is soon overcome, probably because of a tuberculopolysaccharid (14) (15) (16), which is toxic to neutrophiles. These sluggish or dead cells containing tubercle bacilli accumulate even to the point of completely obstructing some capillaries, thus focalizing the tubercle bacilli.

It might be mentioned that Krause regards this initial polymorphonuclear reaction to tubercle bacilli, inoculated for the first time into the animal of experiment, as a nonspecific response to the protein content of the inoculum. The vigor and extent of this cellular reaction are "conditioned" by the amount and concentration of the inoculum. It has long been known that the normal reaction of the animal body to protein set free parenterally is an outpouring of polymorphonuclear leucocytes.

Krause has also pointed out how transient this first polynuclear is accustomed to be unless "dosage" of inoculum is excessive. The body always reacts to *all* suppurating and necrotizing processes with polynuclears in direct proportion to the amount of *tissue* or bacillary protein set free by the breaking-down of tissue. (See Krause's *The Evolution of Tubercle.*)

The next line of defense consists of monocytes which engulf the disintegrating neutrophiles, but a tuberculophosphatide apparently is partially responsible for the early conversion of the monocytes into epithelioid cells (16) (17) (18). Although some tubercle bacilli apparently are killed by the epithelioid cells, others not only live but also multiply. From the dead and disintegrating bacilli, as well as from those proliferating, more products are given off which stimulate the local cells. The waxes cause a proliferation of fibroblasts (2), and the acetone-soluble fat stimulates proliferation of all connective tissue cells (19).

In due time, tuberculoprotein results in an outpouring of plasma (20) about the lesion and later causes sensitization of the body tissues to such an extent that it can be detected by the tuberculin test. In the human body, it is usually stated that the minimum time required for sensitization to become sufficiently developed so as to be detected by the tuberculin test is about three weeks. Wallgren (13) finds that the interval between the entrance of tubercle bacilli into the bodies of infants and the appearance of sensitiveness of the skin varies from three to seven weeks. However, it is impossible to determine this time with a high degree of accuracy, since one is rarely certain as to the exact moment infection occurs or when the bacilli are phagocytosed by the neutrophiles. However, it seems probable that tubercle-formation is well under way before sensitization develops.

Some bacilli are soon carried to the regional lymph nodes, where they are also entrapped and "locked up," in a manner similar to that seen in the primary focus. Apparently, these cellular responses are not due to any specific immunity, since they play similar rôles in "locking up" particles of silica, etc. Thus, the parts involved in tuberculosis of first infection are rather quickly surrounded and encapsulated, and when sensitization of the tissues occurs harm or destruction is confined to these focal areas. Here it appears that we have at least a partial explanation for the benignity of the first-infection type of tuberculosis in the human body.

The reaction of the tissues to tubercle bacilli prior to the time they become sensitive is nonspecific and is practically identical with the reac-

tion to inanimate material of the particulate type. The entire early development of tuberculosis occurs in the human body without symptoms, abnormal physical signs, or X-ray findings. In many cases, apparently, the tubercle becomes fibrosed, and no significant destruction of tissue occurs. In my observations on large numbers of students of nursing and medicine who developed the first-infection type of tuberculosis after exposure to patients, I have never seen one who presented any symptoms before the tissues were sensitized (21). Moreover, I have seen none who presented symptoms subsequently except those who developed reinfection tuberculosis, such as pleurisy with effusion, peritonitis, destructive pulmonary disease, etc.

The entire development of tubercle before sensitization occurs does not result in enough change to produce abnormal physical signs or shadows that can be visualized on an X-ray film. However, in some individuals a pneumonic area appears around the focus of tuberculosis when or soon after the tissues become sensitized. This may be sufficiently large to cast a shadow on an X-ray film or it may be visualized through fluoroscopic examination. It usually causes no abnormal physical signs. Just what enters into the formation of the area which casts this shadow has been a subject of considerable discussion. Some are of the opinion that it is due to tuberculoprotein which is diffused through the walls of the developing capsule and that the reaction seen is no different than that observed in the skin of a sensitized person after tuberculin has been introduced hypodermically.

Sweany (22) holds that it is untenable to consider this area as a perifocal allergic response "because of the even distribution of foci throughout the involved area which means the actual presence of tubercle bacilli, either in reduced numbers or of attenuated virulence." He believes it is possible that this acute pneumonic consolidation may be due to atypical forms of bacilli which are not sufficiently protected to survive and cause typical caseation. He says: "The only other explanation is to assume an inspiration of a few bacilli into each of several hundred foci and around each of which there forms a perifocal reaction."

Wallgren (13) says:

> The end of the period of incubation is thus marked by the appearance of allergy. This condition asserts itself anatomically in the following manner: A rather sudden and violent inflammatory reaction around the tuberculous focus takes place. This perifocal reaction, as regarded histologically, is not a typical

tuberculous process of inflammation but consists of hyperemia with desquamation of alveolar cells, lymphocytic infiltration and edema. Here and there, however, occur minute necrotic foci and giant cells, thus, indicating the etiologic origin of the pneumonic process. The same reaction is produced in the lymphatic glands, which increase rapidly in size.

The introduction of a needle through the chest-wall into the pneumonic area has resulted in the aspiration of tubercle bacilli by Spence (23) and Gorter and Lignac (23a).

The pneumonic area persists for many months, often more than a year, after which it slowly disappears, leaving no trace that can be detected by an X-ray film (24). In the central focus, however, caseation often occurs and in such cases at some later time the location of the focus may be detected even by an X-ray film, through densities cast by calcium and bone which are deposited in the caseous tissue. Excellent descriptions of these lesions have recently been contributed by Reichle (25) and Chown and Medovy (26).

At one time, we looked upon deposits of calcium as an indication of long-standing disease. However, Sweany (27) finds that calcification begins to take place in any closed caseous focus a very short time after caseation. In one patient, five months and nineteen days old, calcium deposits were found, while in two others approximately one year old, there were large amounts of calcium. He observed that in fresh tubercles usually the first evidence of calcium deposits is in the centre of the caseous material. From this point the deposition of calcium often takes place in periodic waves so that rings of calcium are laid down until the capsule is reached. Then there may be resorption and calcification of the inner layer of the capsule or the fibrocytes of the inner layer protrude to the centre of the mass. One rarely sees X-ray evidence of softening of the caseous material with cavitation, as is so often seen when tuberculosis develops on sensitized tissues.

Pagel (28) transplanted caseous tissues into the subcutaneous area of sensitized and nonsensitized animals. In the former group of animals, the caseous tissue softened, while in the latter group it did not. Therefore, he believes that sensitiveness to tuberculoprotein is at least partially responsible for softening of caseous material. Other workers, such as Huebschmann (29) and Jaffe (30), consider sensitization of the tissues an important factor in softening of caseous material. Long (31) states that the chief objection to this view is the fact that in the late

stages of the disease, when there is much softening and excavation, the degree of sensitiveness, as indicated by the tuberculin reaction, may be quite low. Lurie (32) has shown that softening of caseous tissue and the multiplication of bacilli in man is similar in every respect to that observed in animals.

After an extensive study of calcification in the first-infection type of tuberculosis, Sweany (27) says:

In interpreting this process we must bear in mind that the primary lesion is fundamentally different from later lesions. The first mass of tissue that is enclosed has not been subjected to the same action that is met with by secondary tubercles. The allergy that develops later has not had an opportunity to exert its effect upon these cells. So while they become caseated and apparently destroyed, appropriate stains, as pointed out by Ranke will show that the cellular framework is still intact and the elastic fibres are the last to be destroyed. They may be found even in old calcified and ossified tubercles. This partially destroyed tissue, therefore, undoubtedly undergoes gradual lysis from autolytic ferments from within or from enzymes gradually infused from without, and the process of completing the lysis continues. Under the high power microscope, the clearing appears first in small foci—too small to show resolution with any magnification, gradually enlarging until they appear like little globules having clear centres and a dark deposit around the outside, and finally become large and irregular and develop heavy walls, producing a honeycomb effect. The former constituents of the tissue and the caseous material has been autolyzed in these tiny foci and the acids remaining unite with the calcium to produce a precipitate of calcium sulphate and other salts that take the alkaline stains (haematoxylin). The process may be compared to a slow setting of mortar or plaster of Paris, because both reactions may be theoretically derived from the ingredients present.

Puhl (34) and Simon (35) have also observed differences between calcifications in the first-infection and reinfection types of tuberculosis.

Before sensitization occurs in the body, multiple foci of tubercle bacilli may be laid down, and, if brought sufficiently under control before the tissues become sensitive, these lesions will pass through the same stages to calcification as a single lesion. Sweany (22), who has had an opportunity to study such lesions pathologically, is convinced that they are haematogenous in origin

and they may have been laid down during the ante-allergic period of the disease when the allergy-immunity complex has not been well developed. This is manifest, first, because the tubercles resemble the primary type in every way.

There are usually two ages of "primary" tubercles present, a true early single primary and then the many small primary-like lesions. Again the localizations extend evenly all the way to the base. In haematogenous seedings in late reinfection, there is a tendency for the seeding to be more exaggerated in the upper parts of the lungs.

What occurs in the lung by way of development of benign first-infection type lesions apparently also occurs in other parts of the body.

Among northern Negroes we have observed that the body defends itself against the first-infection type of tuberculosis in the same manner as the body of the white person. A few years ago, I had an opportunity to observe X-ray films of the chests of Tennessee Negro children, which showed Ghon tubercle-formation and calcium deposits in the hilum which appeared no different than those seen in the chests of white children of the same state. More recently, I have seen the films of the chests of many Negro children in the Gulf states and these appear to be the same sort of lesions as those of white children. What is seen in the X-ray films of the chests of Negro children is also observed in the chests of Indian children. In viewing the films of the chests of various Indian tribes, we have been unable to see any evidence of difference between their lesions and those of white children (33). However, there appears to be much greater destruction among these races from the reinfection type of disease. It is not at all unlikely that this will eventually be satisfactorily explained on the basis of dosage rather than on that of greater racial susceptibility and lack of immunity.

During the past six years, we have observed the first infection type of tuberculosis as it developed in the chests of a good many adults. These persons have been observed over a considerable period of time before the tuberculin test became positive. We then saw them exposed, after which the tuberculin test became markedly positive, and later, in some cases, the first-infection foci became sufficiently large to cast shadows which could be visualized on the X-ray film. The course of the disease in these cases is apparently no different from that of an infant or child (21). Therefore, it appears that in the various animal species studied and in the human body, regardless of race, nationality, or age, the same defense mechanism attacks tubercle bacilli of first infection, and in the majority of cases in the human body the bacilli are so well under control when allergy appears that very little destruction of tissue occurs unless bacilli are later set free or are taken into the body from exogenous sources and find

lodgment in sensitized tissues where they set up reinfection forms of disease.

As an argument against the sensitization which results from the first infection being a serious factor in the development of clinical reinfection type of tuberculosis, there have been presented cases to show that sensitization does not always develop. For example, one occasionally sees nurses who have worked in sanatoria for the tuberculous five, ten, or more years, and still react negatively to the tuberculin test. While these individuals apparently are rare, yet it does seem quite unlikely that they have escaped the taking of tubercle bacilli into their bodies. Of course, there is always the possibility that bacilli may be eliminated through the secretions of the nose and throat or by way of the digestive tract without having an opportunity to set up foci of disease. Again, one occasionally sees a member of a family who has been exposed to an open case of tuberculosis in the home over a long period of time and still reacts negatively to the test, when all other members of the family react positively. These cases also apparently are rare.

X-ray films of the chest have been reported as showing definite evidence of calcium deposits, and yet the tuberculin test is negative. In such cases, there are several possibilities: In the first place, not all deposits of calcium are due to tuberculosis; second, errors in interpretation of shadows are frequent; third, foci of tubercle bacilli may completely heal, that is, all bacilli are destroyed so that there is no longer any source of tuberculoprotein to keep up the sensitivity of the skin and yet calcium deposits remain. Our great trouble in most such cases is that there is no record of periodical tuberculin testing, so that no one knows whether the tissues were sensitized at some previous time.

One occasionally sees a patient with a negative tuberculin test who has unmistakable clinical pulmonary tuberculosis, with tubercle bacilli in the sputum and cavity-formation, yet the patient is not seriously ill,—in fact, in many such cases there is no illness. These cases are also used to argue that sensitiveness of tissues to tuberculoprotein is not necessary for the development of clinical tuberculosis. Here, again, when inquiry is made about the tuberculin record, one finds that there has been no periodical testing with tuberculin and perhaps the first test administered was fairly recent. Whether these persons were at some time definitely sensitized and have slowly become desensitized, no one knows. However, we do feel reasonably certain that definite desensitizations occur in many cases of grave tuberculosis, such as miliary disease, meningitis, and

in the terminal stages of chronic pulmonary disease, and to some extent in long-standing but less serious cases. Moreover, we must not overlook the fact that the tuberculin test may fail to detect sensitiveness of low degree.

There is a fairly general belief that if a child completely "burns out" the foci of bacilli, after which sensitiveness of the tissues disappears, another invasion of tubercle bacilli from exogenous sources will again result in a benign primary complex. This seems logical, since sensitiveness of the tissues to tuberculoprotein apparently is one important factor for the development of the destructive type of disease. However, we have never seen a child or young adult experience the development of a primary complex more than once.

When examining lesions of tuberculous patients periodically, one often observes sharp contrasts between foci which develop in sensitized and nonsensitized tissues. In a lesion beginning its development in lung tissue of an individual known to be sensitized, there is often evidence of cavitation, following necrosis, caseation, softening and sloughing, making of such an individual a spreader of tubercle bacilli. In some cases, the development of the disease is rapid as one occasionally observes in the infant while in others it is very slow. On the other hand, in lesions which make their appearance in nonsensitized tissues, minimal caseation may occur, but usually does not soften and slough out; therefore, the person with only this type of lesion is a spreader of tubercle bacilli for a very short time or not at all. It is almost unbelievable how much tuberculosis the nonsensitized infant will tolerate with no external manifestations. We have never observed a single case of serious destruction from tuberculosis of the first-infection type. In the light of our observations, we believe that the benignity of the first-infection type of lesion is due in large part to the fact that it begins its development in nonsensitized tissues, that it is well controlled before sensitization appears, and, therefore, is little influenced by the sensitiveness of the tissues to tuberculoprotein which later appears. We have seen many cases pass through these primary-infection stages with no evidence of illness at any time (36). On the other hand, in the reinfection type of disease, we are of the opinion that the sensitiveness of the tissues results in a much more intense reaction from the beginning, that tuberculoprotein causes necrosis of adjacent tissues, and that the necrotic tissue softens, at least partially, because of sensitization, thus, confirming statements by other investigators concerning sensitization as follows:

Krause (37) says:

Accordingly, the allergic reaction is seen to be responsible for all the acute manifestations of tuberculosis, and when so considered it must be viewed as a potent contributor to pathogenesis. Human beings pass as perfectly well as long as they hold their tuberculous infections asymptomatic, inactive. But they are allergic; and any discharge of sufficient focal material to a new place will render them immediately ill because of the allergic reaction that ensues promptly.

Petroff (38) says: "In the past I believed allergy to be a desirable factor and implantation of a few organisms beneficial for the human race, but now I am against such a tuberculization and I believe that allergy may be like a two-edged sword, one edge establishing protection and the other under favorable conditions, bringing about clinical disease."

Korns (39), in speaking of his work in Cattaraugus County, says: "Presumably it is better for young people in this County to grow up with their tissues unsensitized to the tubercle bacillus."

In speaking of native African boys employed in the mines, Cummins (40) says: "The high degree of allergic hypersensitivity in these African mine recruits is remarkable; and the more hypersensitive they are to tuberculin, the more liable are they to break down into acute tuberculosis.

Rich (41) says: "Allergy converts the comparatively harmless protein of the tubercle bacillus into a virulent poison."

After considerable experimental work with *BCG* Clawson (42) says: "These experiments support the belief that without a lesion in tuberculous infection there is no allergy and that an allergic animal is more susceptible to the development of lesions from equal subsequent infections than a nonallergic animal."

There is little doubt that dosage is a significant factor in the development of tuberculosis among infants. Here we may repeat the statement that when we inoculate a laboratory animal with material containing a large number of virulent tubercle bacilli usually no outward manifestations of the disease make their appearance for two weeks or more, yet we know full well that focalization of bacilli has occurred within an hour after bacilli are introduced into the blood-stream and that within twenty-four hours tubercle-formation is well under way, yet no illness appears and no serious destruction occurs until after the tissues become sensitized. Probably because of the large dose of tubercle bacilli which we

have introduced, the natural defense mechanism has been overwhelmed and has not been able to bring under control all bacilli before the appearance of sensitization. Therefore, those which are not under control are free to develop reinfection types of tuberculosis in allergic tissues, and the animal falls ill. Such a situation may obtain in the infant if the dose is sufficiently large. Indeed, this is probably what happened in the Lübeck disaster. Whether or not the *BCG* used in this instance had regained its virulence or another strain of tubercle bacilli was introduced into the bodies of the infants makes no difference so far as subsequent developments were concerned. The dose was overwhelming. Probably most, if not all, of these infants would have controlled virulent tubercle bacilli taken in the ordinary way from a human source as infants usually do. It is quite possible that our rapidly decreasing mortality from tuberculosis in infants in many parts of this country, such as that recently reported by Boynton (43), is due to two facts: First, that more and more infants are being protected from all contamination with tubercle bacilli; and, second, that many of those who become contaminated are receiving smaller doses than in the past and not repeatedly; that is, they are receiving doses which the defense mechanism is capable of bringing under control. The infant's body is small and may be overwhelmed by a dose of tubercle bacilli that an unsensitized adult would easily control. Krause (44) has shown that when proportionate doses of tubercle bacilli are administered to animals, the very young tolerate them as well as the adults.

In some reports, great emphasis has been placed upon the mortality from tuberculosis among infants, and this mortality has been used in opposition to the statement that the first-infection type of tuberculosis is a benign disease and is usually brought under control by the natural defense mechanism of the body. A long time ago, the medical profession gleaned the impression that first infection with tuberculosis is extremely destructive among infants and believed that practically every infant who became infected had a very poor prognosis. This impression was due to the fact that physicians saw for the most part those infants ill from meningitis, miliary disease, or tuberculous pneumonia. Inasmuch as these conditions had usually caused the first outward manifestations, they were assumed to be primary. The more modern use of careful record of exposure, the tuberculin test, and the X-ray film, have proved very conclusively that our original impressions were wrong, and that, when an infant dies from tuberculosis in the acute forms mentioned, death

is caused by reinfection type of disease. In fact, a decade ago, Krause (45) called our attention to the fact that many infants tolerate tuberculous infection well, when he said:

> We may be certain, for instance, that the number of infected infants is several times that of those ill with tuberculosis. Infection tests, performed thus far, indicate that, on the average, about 10 per cent of the general run of dispensary infants of one year of age react positively. Of course, the number dead or ill from tuberculosis at this age is nowhere near this proportion; and these newer facts of the evidence of infection must surely make us revise our older ideas of the extreme gravity of tuberculous infection, as such, for young infants.

Again he said: "The more I see of tuberculosis in infants and the more I confirm diagnosis by the aid of new methods, the more tuberculous infants I find who run along with comparatively little illness and withstand their infection well."

Krause further emphasized the fact that "During 1915 to 1920 the tuberculosis death rate for male infants, from birth to four years, in New York City was 150 per 100,000 alive. The infection incidence was surely as high as 10 per cent or 10,000 per 100,000. On this basis, it would appear that only one of every 66 infected male infants died from tuberculosis."

Drolet calls attention to the fact that until recently in many places, the tuberculosis mortality rate was highest during the first year of life but that now the picture has been radically altered. In 1868 in New York City, the mortality among infants was 1,000 for each 100,000 living. In 1900 in the ten original registration states, 350 male infants under one year of age died of tuberculosis for every 100,000 living, but by 1929 the mortality rate for male infants had dropped from 350 to 58. Among female infants in 1900, 295 died of tuberculosis per 100,000 living, but in 1929 this figure had dropped to 52, while the rate for young women between 20 and 25 years was 120 per 100,000 living in 1929. Drolet (46) points out further that by 1932 for the first year of life in the United States, the mortality from tuberculosis was only 39 per 100,000 infants living, whereas, between the ages of 20 to 25 and 25 to 30, the mortality was 83 and 90, respectively. Thus, from 1868 the mortality among infants had been reduced from 1,000 per 100,000 living to 39.

While the number of infants and children who die of these fatal forms of reinfection type of tuberculosis seems to be large in some groups

reported, we now know that they represent only a very small percentage of the infants who have developed the first-infection type of tuberculosis; that the vast majority bring their lesions under control and have few or no external manifestations of the disease. In fact, in 1926, we called attention to the great powers of the infant in resisting tuberculosis (47). Our observations have continued and after fifteen years they show that only a small percentage of the infants who had first-infection type of tuberculosis died of tuberculosis in infancy or early childhood. Moreover, it has been known for a long time that the greatest destruction from tuberculosis occurs in adult life. Krause says (45): "As it works out in life, it is beyond dispute that the ravages of tuberculosis are in every way greater in later life than in childhood; and, even allowing for differences of environmental factors that determine illness, we would consider the proposition of a higher adult resistance as unproved."

We have recently reported 206 cases of first-infection type of tuberculosis detected in the pneumonic stage in infants and children (36). The course of these lesions has been approximately the same in every case, whether treated or not. In 155 of these children, some of whom have been observed since 1921, the lesions have reached the calcified stage or evidence of fibrous strands is present. One hundred and thirty-six of these children have recently been traced and reëxamined, and all are apparently normal, healthy individuals. Two of this group had considerable temperature elevation, lasting for a few weeks when the disease was in the pneumonic stage. With these exceptions, there has been no incapacity from first-infection type of tuberculosis in the entire group. Fifty-one of our 206 infants and children with disease in the pneumonic stage have not yet shown evidence of calcification in the lesions; indeed, some of the lesions have not yet completely resolved. One of these children, whose pneumonic first-infection type of tuberculosis was detected in 1923 when six months old, had a reinfection type of bone-and-joint tuberculosis at the age of eleven months, and died of reinfection tuberculous meningitis at seventeen months. Another infant at the age of ten months with first-infection type of tuberculosis in the pneumonic stage had also at the time of the first examination what was interpreted as miliary tuberculosis involving both lungs. This child has never been ill. The pneumonic lesion is coming under control in the usual way. The evidence of miliary disease on the X-ray film is gradually disappearing. If our original interpretation was correct, the miliary disease probably developed before the tissues were sensitized. Where can any-

one find a series of consecutive cases with reinfection type of pulmonary tuberculosis sufficiently developed to cast definite X-ray shadows with such a benign course?

One may insist that the resistance of the human body to tubercle bacilli is raised through the development of the first-infection type of disease, but the fact remains that it is the reinfection type of disease, whether it attacks the meninges, the lungs, the bones and joints, or any other part of the body, that causes the morbidity and the mortality in the human family, whereas, the first-infection type of disease, *per se*, causes little morbidity and almost no mortality. If we could not show a better record for immunization against smallpox, diphtheria and typhoid fever through our present methods than we can for tuberculosis through first infection, further efforts in this direction would be unjustified.

Not long ago, we taught students of medicine that an attack of cervical adenitis in childhood was almost a guarantee against pulmonary tuberculosis in later life. However, longitudinal studies of such cases have disproved any such belief. Miller (48), after making careful observations says that

> one must remember that while the tubercle in the lymph nodes in the neck may be conferring on the organism an added degree of resistance, they are at the same time harboring living bacilli which may be set free at any time to be carried to other parts of the body, there to grow in increased numbers.
>
> We must be guarded in accepting any such generalization as that tuberculous cervical adenitis may confer any practical immunity to tuberculosis elsewhere in the body. It will give rise to changed reaction and a heightened resistance, but this is probably of not enough actual potency to warrant our accepting it with complacency.

Tuberculosis takes a place in the front line of communicable diseases. Experts in this field state that among large numbers of unvaccinated persons coming in contact with cases of smallpox, in the neighborhood of 75 to 80 per cent will contract the disease. In the case of tuberculosis, it will range between 80 and 100 per cent; that is, this high percentage of exposed persons develop the first-infection type of tuberculosis, as manifested by the positive tuberculin reaction.

We know that far more clinical tuberculosis develops among members of families who have been exposed to an open case of tuberculosis in the home than among members of other families not so exposed. We know that more tuberculosis develops among the consorts of tuberculous

patients than among other persons in the general population. We know that more tuberculosis develops among student nurses and recent graduates of schools of nursing, who have been exposed to open cases of tuberculosis, than among girls of the same age in the general population. Tuberculosis workers of this country are fairly well agreed that contamination with tubercle bacilli at all ages of life should be avoided, because we know that the first-infection type of tuberculosis sets the stage for subsequent developments, as expressed by Wallgren (13): "The part played by primary tuberculosis is not, of course, exhausted by the manifestations I have mentioned for, indirectly, primary tuberculosis is the starting-point also for tuberculous diseases of a quite different nature, such as meningitis, pleurisy, miliary tuberculosis and last, but not least, tertiary pulmonary tuberculosis." A similar expression by Smith (49) is significant: "As a matter of fact, there can be no infection without disease since infection with the tubercle bacillus means that it has lived and grown in the body of its host and has set up its characteristic pathological lesions. No matter how small, how deeply seated, how obscure such lesions may be, they always carry the threat of serious results from dissemination." Once we allow the first-infection type of tuberculosis to become established in the body of an infant, child, or adult, it is beyond recall. As yet, we have no practical method of desensitization or do any of our therapeutic procedures destroy tubercle bacilli within the body. Krause (50) says: "For months, years, decades, or even through the span of a normal lifetime, these abnormal formations, with pent-up living tubercle bacilli, abide within the tissues." Therefore, the major part of the campaign against tuberculosis, both in animals and man, has been fundamentally sound, since its chief aim has been to prevent contamination with tubercle bacilli.

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PREGNANCY AND TUBERCULOSIS

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It would seem that this, a subject of such importance to so many living people and to those as yet unborn, has been more or less neglected during the last few years. Until recently, a wealth of ideas, observations, and opinions have been given and published, almost all of which, in the light of to-day's understanding, are chiefly of academic interest, have outlived their value, and might well be discarded.

In this modern age of reform and evolution, in a world overflowing with every kind of half-baked theorist shouting his doctrines from the housetops, and strangely enough being followed and supported by a multitude of the same kind, is it any wonder that eugenists and birth-control enthusiasts attempt to solve our medical problems for us?

It is only to be expected, in these times, when prevention or interruption of pregnancy from purely selfish or economic reasons is looked upon as a most logical plan and a procedure so universally exploited and taught by lay organizations bent upon dictating to our profession, that thumbs would be turned down on every pregnancy occurring in a tuberculous woman.

One of the two greatest influences against wild and uncontrolled birth control and abortion has been the medical profession. However, until the obsolete and erroneous teachings so generally accepted by the majority of our members are corrected, as to the hazards of pregnancy in the tuberculous, we may expect no different understanding of this very important matter.

If we pause for a moment to reflect upon the illustrious names on that long list of those geniuses who have been tuberculous, we can readily see that to deny the offspring of such mental giants the right to be born would, indeed, be short-sighted and unwise. Especially so, since this denial would be founded on the dogmatic and outlived beliefs of the danger of pregnancy to the phthisical. And again, because the offspring of these same sufferers from disease are born into the world as free from hereditary taint and with as good a promise of health as the children of more fortunate mothers, gives another reason against such a belief.

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When we consider the medical literature of to-day, text-books written and used as reference works for medical students, we are surprised at the apparent lack of a modern viewpoint on this matter.

In one of the later works on gynecological and obstetrical tuberculosis, Norris (1) gives the following opinion:

> The deleterious influence of pregnancy on tuberculous women is well known, and many theories have been advanced to explain this fact. During pregnancy the woman carries a double load, and as the gestation advances, the drain upon her strength becomes more and more marked. . . . The author believes that further study of this subject is required to explain why so many cases of early pregnancy show an exacerbation of the tuberculosis.

This excellent work devoted to the above subject contains an extensive literature, the greater part of which was written prior to 1919, although a supplementary section shows numerous articles written as late as 1929.

A search through the cumulative author and title index of the *Transactions* of our National Tuberculosis Association from 1921 to 1930 does not show a single work on this matter, with the exception of a timely article by the late Carl A. Hedblom (20), recently published in a review of the literature, which finds 22 cases of women following thoracoplasty who have successfully borne children.

A recent editorial by Allen Krause (2) calls attention to several points which should be of great value in clarifying the subject and lessening the confusion that now exists.

He writes that the very fact that the term pregnancy is used indiscriminately with no distinction as to what phase of the puerperal state is meant, pregnancy, parturition, or puerperium, nor its particular influence on the disease makes the problem all the more complex. The statistical data vary to such a degree with the authenticity of data, keenness of diagnosis, the statistician's ability, the age of the mother, stage of the disease, and the number of pregnancies undergone. He brings out that well-known experience of all, that, in apparently normal women, there are those to whom pregnancy, a physiological process, is a boon, and who improve and thrive with it to reach the fulfilment of normal motherhood, and, on the other hand, those in whom, almost from the outset, pregnancy becomes a pathological condition, fraught with the utmost danger to the mother. If we take such examples and add to them tuberculosis, we are most certain to expect parallel results. May it not be that pregnancy exerts a harmful effect on tuberculosis in those women, who without

tuberculosis, would naturally tolerate pregnancy poorly, and a harmless, and even a beneficial, effect on those tuberculous women, who, without tuberculosis, would stand pregnancy well, or even have their bodily economy improved by pregnancy? He further states there have been numerous contributions to the general thesis that actively tuberculous women have their tuberculosis improved during pregnancy.

It would appear to those who have given much thought to the matter, that the above observations are only too true. Here is a patient,

> a strong and raw-boned Irish woman, thirty-three years old, with 3 children, 6, 8, and 12 years old, entering the Sanatorium with a productive, cavernous lesion of the right upper lobe. She remains here four months, the lesion quiets down, and the cavity closes. She gains 65 lbs. in weight, and returns home. In a period of six or eight months, she starts to take care of her family and house. During the next four years, against advice, she brings three more children into the world. The last and final pregnancy, in a woman taking care of five children, in addition to the general housework of her home, proves too much for her: the tuberculosis lights up and progresses to a fatal result, two months subsequent to her last labor.

While pregnancy no doubt marked the beginning of the last act of this little drama of life, it could not be blamed, *per se*, for the disastrous ending of such an unusual obstetrical and tuberculosis picture. No one by the wildest stretch of imagination could expect anything else but this result after such flagrant disregard for the capabilities of the human body.

The opinions of the French writers are well understood, from the report by J. Stiassne (3) from a symposium at the *Academie de Médecin* and the *Société d'Obstetrique*, in July, 1930. Up to the end of the nineteenth century pregnancy was generally believed to have a favorable effect on phthisis. Since then, following works of Moriceau, Louis, and Dubreuilh, the opposite opinion has been maintained, and the discussion continues. In general, pregnancy and labor exert an unfavorable effect on tuberculosis, and add an extra hazard to the prognosis. However, in actual practice, aggravation is more or less to be feared, according to the type of the disease.

The idea that pregnancy was a process beneficial to tuberculous women was held from very early times, Cullen (13) (1712–1790) believing this experience often ameliorated the disease. Sabourin (4), in 1918, recommended marriage for tuberculous girls because it endows them with a certain degree of immunity.

On the other hand, many writers have published statistics and opinions, mainly opinions, to the effect that it is very dangerous for a tuberculous woman to become pregnant, irrespective of the type of the disease with which she is affected. Experimental evidence has been adduced to this effect.

Thus Herrmann and Hartl (5) infected gravid and nongravid guinea pigs with tubercle bacilli. They found that the infected pregnant animals fared very badly, when compared with those not pregnant. To the contrary, Müller, repeating the same experiments, found that the nonpregnant died earlier than the pregnant animals. In fact, his studies showed that infection with tubercle bacilli had no influence on the foetus, because no animal aborted, and the newborn were as healthy as could be expected.

Thus, it has been pointed out by Schultze-Ronhof and Hansen (6), in a most exhaustive review of the subject, that animal experimentation has not solved the problem of tuberculosis in pregnancy.

More recently, numerous articles published by internists, capable of classifying and interpreting the results of such studies, have shown that little, if any, effect is produced by pregnancy in large numbers of cases of tuberculosis. A study of this problem by Ornstein and Kovnat (7) of 5,470 tuberculous, nonpregnant females, against 85 pregnant and tuberculous women, showed that the pregnant, apparently, had somewhat the better outcome. The death-rate in the two groups was almost the same.

Again, in the same journal, an article by Jennings, Mariette, and Litzenberg (8) quotes Weinburg (9), Van Tussenbrock (10) and Alice Hill (11), stating that they have all gathered material from separate clinics, where they were able to compare pregnant tuberculous with nonpregnant tuberculous women, and all report that tuberculosis in the two groups ran practically parallel courses. Their study points to certain facts: first, the necessity of adequate treatment for the pregnant tuberculous woman, and, second, that, if adequate treatment is given, a therapeutic abortion, because of pulmonary tuberculosis, is rarely indicated.

A biometric study by Jennings and Mariette (12) of 470 cases of tuberculous women, of whom 80 bore children, reveals much the same results. These indicate that cases of those who have borne children and of those women who were never pregnant are not differentiated in tuberculosis, with respect to improvement, etc., and unimprovement, etc. They conclude that pregnancy does not have a marked effect on the progress of

tuberculosis. The evidence is striking that the phenomena are independent of one another.

Fishberg, quoting Forssner (13), found that 801 nonpregnant, tuberculous patients were no better off than 133 who became pregnant. He believes that the sinister influence of pregnancy on pulmonary tuberculosis is a dogma—a tradition founded on unreliable information.

Referring again (13), it is mentioned that all carefully collated statistics, by those who are qualified to pass upon the character of the lesion in the lung, show that the number of reactivations of the process during and after the pregnancy, is not much larger, if at all, than might be expected had they not become pregnant.

It has been suggested that after labor the diaphragm descends and thus favors aspiration of tuberculous material from the upper to the lower lobes. This may partly be so but does not explain those cases in which most of the active involvement is primarily in the lower lobes. However, the diaphragmatic ascent or descent is very likely one of the greatest factors in both the improvement in the later months of pregnancy of the tuberculous, as well as the subsequent postpartum progression of the disease which sometimes occurs.

This point, so important, and to which so little attention has been given, the phenomenon of alternate prepartum improvement, and postpartum retrogression, was also noted and called to my attention in 1920 by Richard J. O'Shea of Seattle (14), who, after delivery of tuberculous mothers, always applied the abdominal binder as tightly as possible, almost uncomfortably so. The breast-binder he also applied in a similar manner, this for the primary purpose of hastening the drying up of the milk, but which aided in putting pressure on the chest-walls, and thus resting the lungs. So, an obstetrician, without any particular interest in pneumothorax or collapse therapy, through keen observation and study, approximated, as closely as he could, what the phthisiologist had been attempting by specialized methods of mechanical rest.

This is very likely the reason that those pregnant women who go through pregnancy with a successful pneumothorax or phrenic-nerve operation so infrequently show extension of their disease.

The pneumothorax cases which, under my observation, have done badly following pregnancy, are only those in whom the collapse was unsatisfactory, or in whom, for some unknown reason, the pneumothorax had been discontinued some two or three months prior to parturition.

A factor of considerable importance in the spread of the disease following labor is the physical effort of labor itself. The same result we would expect in any tuberculous patient who would suddenly indulge in violent physical exercise. Straining, with the increased pressure on the lung, accompanied by a more rapid flow through the blood and lymphatic channels, with deeper breathing by the patient, no doubt favors aspiration into the circulatory systems of tubercle bacilli or the by-products of tubercle. Then too, should be considered their possible entry into the uterine sinuses from tuberculous areas on the placenta, following its separation during labor.

These are possible causes for the cases of miliary tuberculosis which are sometimes discovered in women soon after child-birth. The author has seen several such cases, with negative histories of tuberculosis, no physical signs or roentgen evidence of any previous gross pulmonary lesions, all of whom were diagnosed one to three weeks following labor.

Carrell (18) of Tucson, Arizona, in a community where perhaps a larger percentage of his obstetrical cases are tuberculous than would be elsewhere, in order to prevent some of the aforementioned dangers in the tuberculous pregnant, has devised a specialized technique for handling these patients.

Charles Shannon (19) of Seattle, whose patient, R. G. is referred to later, was asked why he allowed the patient, after such a stormy first pregnancy to go through two more when so many obstetricians believe that pregnancy seems to have ill effects on tuberculous women.

His reply was to the effect that in his opinion patients, whose disease had been arrested for two years or more under ordinary conditions of life, were probably no worse obstetrical risks than normal women, and that he found that those patients who could receive adequate treatment seemed to do about as well as the nontuberculous, provided overwork and other such factors could be avoided.

It is a common observation of tuberculosis specialists and obstetricians, especially in exudative-caseous types of pulmonary tuberculosis, that a rapid breaking down of these areas, with quickly developing cavities, sometimes occurs following labor.

In submitting the following explanation of the causation of rapid breaking down of tuberculous tissues in these patients, it should be stated that these ideas are purely theoretical, and not based upon any experimental evidence or special work along these lines, but founded only upon the

observation of many tuberculous pregnant women, with a study of the unfortunate results sometimes seen. It is hoped that these suggestions might be thought worthy of further study.

We know that the blood of pregnant women contains a protective, proteolytic ferment, specific for that protein, namely placental, which caused its formation. On the basis of this fact are founded the numerous biological tests for pregnancy.

Aschheim (15) states that

> the basis of the biological pregnancy test lies in the quantitative, and not in the qualitative hormonic differentiation of the blood and urine of pregnant women as contrasted with the blood and urine of nonpregnant women. This difference is so exceptionally great that it may be the outstanding characteristic of the blood and urine in pregnancy. During the later months of pregnancy the amount of oestrum-inducing principle increases markedly, especially in the urine, so that at this stage from ten thousand to forty thousand mouse units may be found in a litre of urine. . . . It appeared from these studies that the substance which we were able to demonstrate in pregnant women was not of hypophyseal origin, but was produced in the placenta. . . . In general, the excretion of gonad-stimulating substance ends by the tenth day, but in some cases positive reactions may be found as late as the sixteenth day.

As Aschheim has stated above, these hormones are produced in very large quantities, 3 cc. of urine being sufficient to give a positive reaction quite early, and are specific for placental, decidual or similar tissues. Furthermore, as has been stated, it is generally believed by workers in tuberculosis that in pregnancy cases in which progression of the disease occurs, this sometimes happens in the latter part of the pregnancy, but more often soon after delivery of foetus and placenta.

So, with a specific proteolytic ferment present in large quantities in the body fluids, the placenta which caused its formation, having been removed from the uterus, what effect on sensitized lung tissue might not this free substance have? While Aschheim has shown that this hormone is eliminated within probably sixteen days, has not enough time elapsed to allow such a destructive action, if this be the case, to be initiated and to cause this rapid breaking down as has been so frequently observed?

To cite Williams (16), the pregnant uterus, a muscular organ, after parturition weighing about 1000 gm. (over 2 lbs.), within a week decreases in size and weight to about 500 gm. At the end of involution, about six

to eight weeks, it has further decreased in weight to about 40 to 60 gm. (about 1 to 2 ounces). Thus from the body there has been removed almost 1000 gm. of material, the greater part of which is pure protein. The removal of this is accomplished by the action of proteolytic enzymes, which are probably specific in action. After the breaking down of these substances, their elimination is chiefly through the kidneys in the form of nitrogen, 7 to 9 gm. of which are removed during the first twenty-four hours following delivery. On the third or fourth day the elimination of nitrogen is increased by about 40 per cent.

It has been shown by Slemons (17) that, following the Porro-Caesarian operation, such a nitrogen output by the kidneys does not occur, and such a high output of nitrogenous substances as does follow childbirth is chiefly from the breaking down of uterine protein.

On the basis of the above circumstances, there are two possible factors which may have some bearing on the disintegration of sensitized lung tissue in tuberculous women following childbirth. There may be, first, the breaking-down of lung tissue from the presence in the blood-stream of considerable quantities of uterine protein, suddenly released, whose effect may be similar to that following the introduction from without of a foreign protein. The mechanism of these changes is very likely much the same as the specific localized result observed after the sudden invasion of the blood-stream with tubercle bacilli or the products of tubercle. Second, it is possible that a distinct and disintegrating effect may be produced at the lesion from the action of the specific proteolytic ferments present, no doubt in large amounts during the stage of involution, and, following this, in a free and uncombined state. And how soon afterward, as in the case of the specific placental hormone of sixteen days, do these uterine proteolytic bodies disappear?

The following case reports show the after-effects of collapse therapy in 4 patients several years after the discontinuance of all therapeutic measures, and may minimize the fear so often held by layman and physician as to the dangers of pregnancy in the tuberculous.

In one patient there were so many complicating circumstances and the patient was so desperately ill, that the whole clinical picture was almost hopeless from the very beginning. Yet this same young woman, eleven years later, living in Juneau, Alaska, in a climate not considered any too good for tuberculosis, writes me of her good health, is raising her child, and, free from all signs of tuberculosis, in addition, taking care of her home.

1: The patient, E. Z., a young married woman of 20, was sent to the Riverton Sanatorium on September 15, 1924: six months pregnant, with an active exudative and cavernous tuberculosis of the left upper lobe and upper part of the left lower lobe and right upper lobe, and giving a history of a former pleurisy with effusion which had been aspirated a few months previously (figure 1). She was a well-nourished girl of Russian extraction, very fair, thin-skinned, and of the type that one usually associates with low resistance to phthisis. Pneumothorax was attempted, but, on account of adhesions from her former effusion, only a small amount of air could be introduced at one time, never more than 150 cc. These small refills were continued until the pregnancy was over, but, on account of the general condition of the patient and the apparent uselessness of this form of therapy, it was discontinued. At term she was delivered of a normal 6-lb. daughter, who was immediately removed from the mother. The delivery and puerperium were normal in every respect, except for the presence of albumin and casts in large quantities in the

Case 1

Fig. 1. E. Z. September 10, 1924. Admission to Riverton Sanatorium; six months pregnant.

Fig. 2. E. Z. June, 1925. After first stage of thoracoplasty.

Fig. 3. E. Z. August, 1935. Nine and one-half years after admission.

Case 2

Fig. 4. R. G. June, 1928. School girl, 16 years of age.

Fig. 5. R. G. May, 1931. After first pregnancy.

Fig. 6. R. G. September 23, 1932. Discontinuance of collapse. Two pregnancies since.

mother's urine. This had existed for several weeks prior to parturition, and after this there was an increase in the urinary findings. This renal complication lasted for several months. Two cavities developed in the left upper lobe about a month following delivery, and the patient was raising about 60 cc. of sputum daily, when there began a persistent colicky diarrhoea, the stools being watery and later containing mucous flakes and blood.

Before more destructive changes had occurred it was decided to attempt surgical collapse of the lung and accordingly a lower lobe thoracoplasty was performed in 1925 (figure 2), four months after parturition. As the bowel condition grew progressively worse, it was decided to postpone the next stage of her thoracoplasty. A gastroenterological study revealed rapid emptying of the colon, loss of haustral markings and ragged contour of the caecum, while the patient was having fifteen to twenty watery stools daily.

Accordingly, a diagnosis of tuberculous colitis was made, and, in order to give this young woman what small chance there remained, a two-stage ileos-

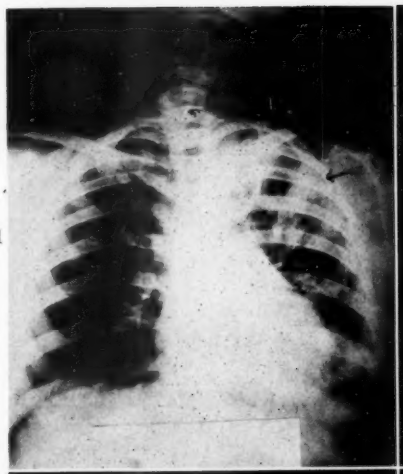

Fig. 1

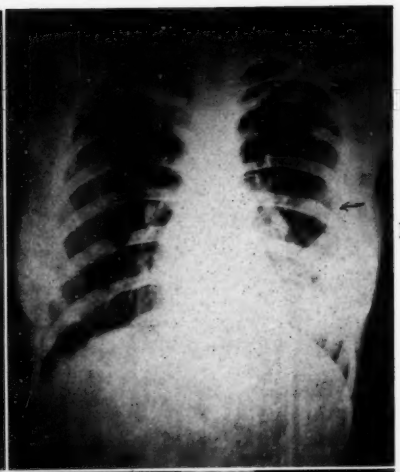

Fig. 4

Fig. 2

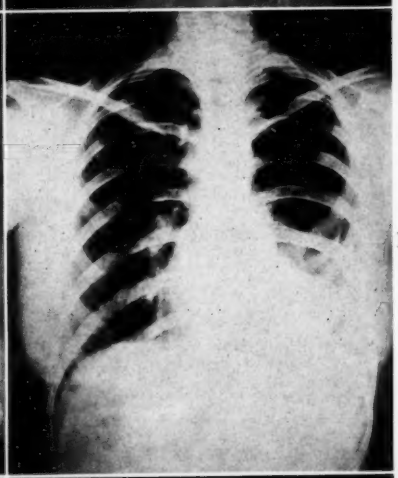

Fig. 5

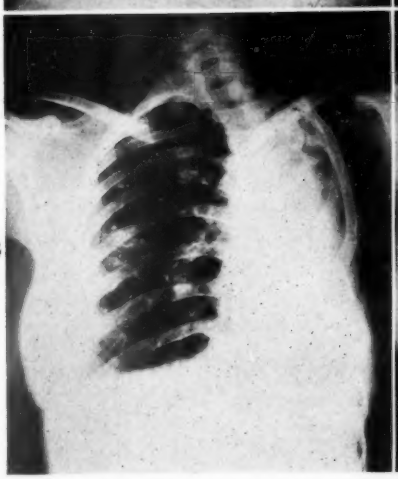

Fig. 3

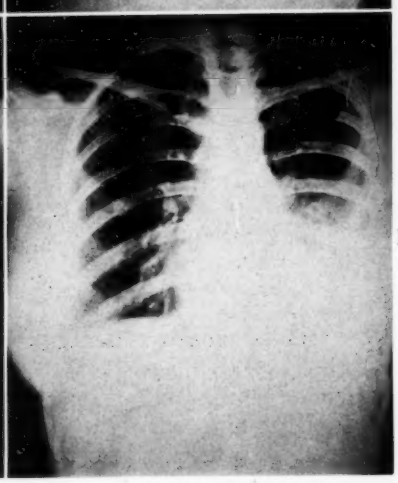

Fig. 6

tomy was done under local anaesthesia. This was made with a minimum of trauma and the ileum was opened about four inches proximal to the ileocaecal valve. These points are mentioned as it is believed that the technique in the surgical treatment of tuberculous colitis makes the difference between success of failure. This fact was so well emphasized by the very successful results of that master-surgeon, the late Dr. Coffey of Portland.

Almost immediately, following this last operation, the patient improved. She began to eat better and gain weight, her urinary findings lessened, and her temperature began to fall. Cough and sputum, however, remained about the same. This operation was done in September, 1925.

In April, 1926, the patient's condition had improved to a great extent, but there was still about 40 cc. of sputum daily. In May, 1926, the last stage of the extrapleural thoracoplasty was performed, the upper 6 ribs being removed.

The patient responded very well to this last operation, and from this time on continued to improve. The urinary findings cleared, cough and sputum stopped, a gain of about 30 lbs. was made and in January, 1927, she was discharged from the sanatorium with her pulmonary disease apparently arrested. This young woman was seen in August, 1935, when examination was made (figure 3). Except for a severe cold, which caused her to run for a few weeks a slight fever and made her somewhat anxious, she has been quite well.

An X-ray taken within the last month shows the collapsed lung well fibrosed and with many calcifications of the contralateral lung. The physical examination discloses no râles and her case seems arrested. It would appear that collapse therapy, with surgical drainage and rest of the diseased bowel, have produced an arrest of the tuberculous processes, and that pregnancy, even in such a case, did not prevent its fulfilment.

2: R. G., a school-girl, aged 16, of Irish descent, first seen in June, 1928, with an exudative lesion and cavity of the left lower lobe and epituberculosis of the right lung (figure 4). She spent the next two years in a sanatorium where artificial pneumothorax was done shortly after her admission. After her discharge this collapse was continued at my office for the next two years, and during this period she was married, still continuing her pneumothorax refills.

During the last few months prior to her marriage, the lung had been allowed to expand partially, in order to observe any untoward signs or symptoms which might develop. Since none appeared, and the usual pneumothorax was continued afterward, the patient was warned not to become pregnant for the first year.

Nevertheless, within the next few months she became pregnant and had decided to let the pregnancy take its normal course. The pregnancy seemed natural; the usual refills were given every month up until the 6th month, when the amount of air introduced was gradually lessened. The refill in the 8th

month was about 100 cc. There was no dyspnoea present, in spite of the rise of the diaphragm with the pregnant uterus. Near the last month of gestation, the patient became violently ill and was taken to the hospital with persistent vomiting and pains. The urine showed pus cells, and, after a renal study, a diagnosis of acute pyelitis was made. No tubercle bacilli were discovered in the urine, nor by guinea-pig inoculation. During the next two weeks the pernicious vomiting continued; the patient rapidly lost weight, and her temperature rose to 104°, and remained so. X-ray of the chest (figure 5) was made to determine whether a lighting-up of the lung focus had occurred with a possible miliary spread, but this was found not to be the case. No râles were present, nor had any cavity been opened by allowing the lung to reëxpand partially. Finally, after two weeks the patient went into labor, and a five-pound dead baby was born. The patient had stubbornly refused to allow premature labor to be induced previously.

The following day, 200 cc. of air was introduced into the left side, which was followed two days later by a similar refill. Following the emptying of the uterus, the temperature fell to 101°, and after the second pneumothorax it remained below 101° for about a week. A third refill was given in a few more days, and after that every four days until complete collapse was obtained. The patient went on to a complete recovery from the pyelitis, her urine being free from pus cells within two weeks. The pneumothorax was continued for another year, when the lung was allowed to reëxpand (figure 6); and meanwhile the patient has gone successfully through two more pregnancies. She now has a child three years old and a fourteen-month-old baby.

Three years have elapsed since her lung has reëxpanded. She is now living the normal life of a young housewife, taking care of her children, and shows no evidence of her former disease.

3: This patient came to Riverton Sanatorium, April 12, 1930, (figure 7) five months pregnant, the left upper lobe showing productive cavernous tuberculosis, with a cavity, 2 cm. in diameter, below the 3rd rib (figure 7). Her sputum was positive, and she gave a history of three hemoptyses of 30 cc. each during the week before.

This young Greek woman, A. C., aged 23, and 5 ft., 5 in. tall, was a large, buxom girl weighing about 160 lbs. Two days after admission, pneumothorax was begun 175 cc. being introduced and followed the next day by a refill of 250 cc. Within ten days, a satisfactory collapse was obtained, the upper lobe cavity being completely closed (figure 8). The patient remained in the sanatorium until the week before the date for parturition, and was then taken to a general hospital, where a normal delivery brought her a 9-lb. boy. During the last three months of her pregnancy, the amount of air at refills was gradually reduced from 500 to 250 cc., just enough to maintain under fluoroscopic

control the pneumothorax pocket, and yet of a size not sufficient to produce any sensation of fulness or tightness in the chest (figure 9).

About one year ago this woman gave birth to a second child, an 8-lb. girl, the pregnancy and labor as well as puerperium being normal in every respect.

Since this time the mother has enjoyed good health, is taking care of her home and children, and apparently is an arrested case.

4: N. M., aged 29, housewife, was first seen by me in July, 1930, with an old bilateral fibroid tuberculosis of both upper lobes of nine years' duration. The patient had a small cavity in the left upper lobe from which she had recurrent haemorrhages of 30 to 90 cc.

Pneumothorax of the left side was attempted, but discontinued later, as the refills were insufficient to produce a satisfactory collapse; and about a year later a temporary phrenic-crushing operation was performed (figure 10). This caused a three-inch rise of the diaphragm, which lasted about 5 months,

Case 3

Fig. 7. A. C. April 2, 1930. Admission; five months pregnant.
Fig. 8. A. C. May 4, 1930. Pneumothorax closure of cavity.
Fig. 9. A. C. October 21, 1932. Reëxpansion of lung. One pregnancy since.

Case 4

Fig. 10. July 2, 1931. Before phrenic operation.
Fig. 11. August 29, 1931. After operation. Rise of diaphragm.
Fig. 12. March 26, 1932. Pregnancy in 1934.

as meanwhile the patient gained considerable weight and became much improved (figure 11). A few months later she passed from my hands (figure 12), moved elsewhere and became a Christian Scientist. I learn that she has since gone through a pregnancy, has a baby about a year old, leads a normal life, and is apparently well.

Accordingly, in considering these 4 cases, the first, with a disease the type of which we look upon as one of poor prognosis and complicated with severe manifestations, is alive and apparently well eleven years following the diagnosis of her disease and nine years after her last thoracoplasty. The second, going through pregnancy with a good pneumothorax collapse of her lung, yet developing in the last month a severe pyelitis and pernicious vomiting, is alive and her disease arrested seven years following the onset of her trouble and three years after her labor, and has since successfully passed through two more pregnancies, the last one 14 months ago. The third patient, with a more favorable type of

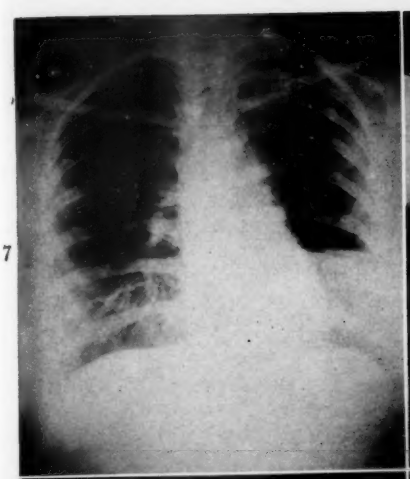

Fig 7

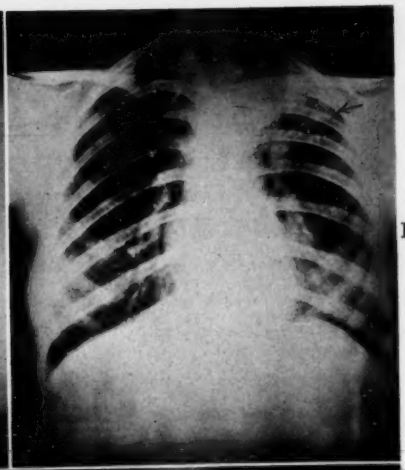

Fig. 10

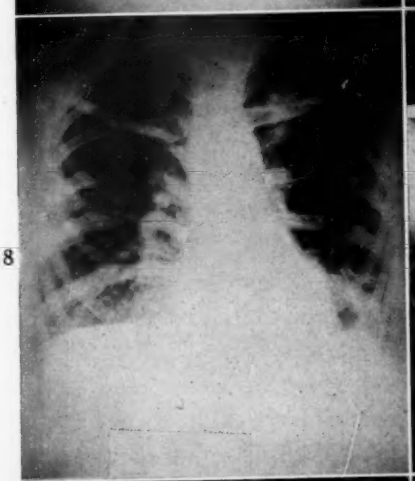

Fig. 8

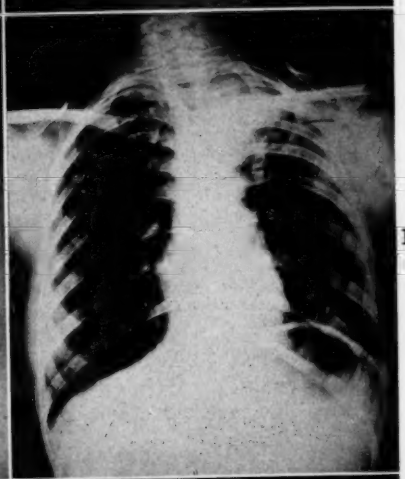

Fig. 11

Fig. 9

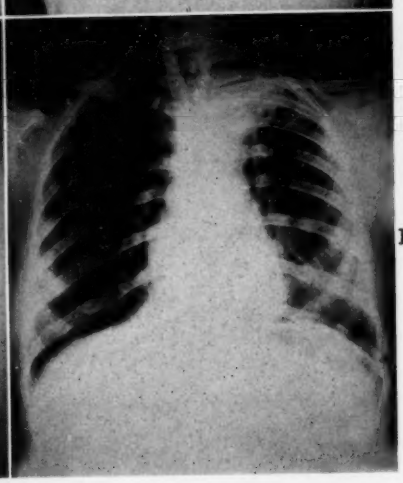

Fig. 12

tuberculosis and with a pneumothorax induced in the latter part of her first period of gestation, has in the meantime borne a second child and is, to all intents and purposes, perfectly well one year following this last labor. Within a period of five years, this patient has had her tuberculosis become arrested and has successfully completed two pregnancies.

The last case, five years later, after ordinary rest-cure and phrenicotomy of two and one-half years' duration, has undergone pregnancy and, as far as I am able to learn, is leading a normal life and is apparently well.

SUMMARY

1. After a careful perusal of collected studies by qualified observers who have investigated this problem from various sides as to the type of the disease, stage, and end-results, and with the author's own experience of long observation of many pregnant tuberculosis cases, it is believed that the risk of pregnancy for a tuberculous woman is no greater, if she be properly treated, than for the nontuberculous pregnant patient.

2. Those who become pregnant should have sanatorium care under proper careful direction; and, if possible, some form of selective collapse therapy should be carried out.

3. After labor treatment for tuberculosis should be carried on vigorously, and no successful form of therapy be discontinued too early, and, in any event, only after careful study by one who is qualified in the handling of such cases.

4. A closer working relationship between the obstetrician and the phthisiologist will not only bring a greater measure of success to the physicians themselves in the management of such cases, but will save the lives of many which might be sacrificed without it.

5. Therapeutic abortion is rarely, if ever, indicated in these patients, and certainly should not be carried out after the fourth month of gestation, when the operative risks become practically as great as those of full-term delivery.

6. Some theoretical suggestions are made above as to the cause and mechanism of the rapid destruction of tuberculous lung tissue which sometimes is observed in women late in pregnancy or following parturition: this, with the thought that more observation and study may be made along these lines by those who, through ample laboratory and clinical facilities, are in a better position to do so.

It is desired that this most important question of pregnancy and tuberculosis will be given more attention, not only by those who practise the

treatment of tuberculosis but by that larger group who engage in the art of obstetrics;—to the end that the lives of these unfortunate women may be preserved, and that they may enjoy the fulfilment of the experience of motherhood, so that the lives may be saved of numberless infants who may bear in them the blood of the truly great.

With a better and more intelligent understanding of the problem, and with proper management, we shall see these young women emerge from an experience, once looked upon by most of us as most dangerous and unjustifiable, almost if not quite as safely, and successfully, as their more fortunate sisters.

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THE INCIDENCE OF INTESTINAL TUBERCULOSIS[1]

BENJAMIN L. BROCK AND GILBERT O. PERRY

We have been impressed that the incidence of Intestinal Tuberculosis is definitely on the decline. For this reason and also in order to make some comparative observations relative to this disease in both the white and negro races this study was undertaken.

Since 1927 the Waverley Hills Sanatorium has employed the technique described by Brown and Sampson in their *Roentgenological Diagnosis of Intestinal Tuberculosis*. With the exception of a comparatively few terminal cases all patients are routinely examined according to this method shortly after admission to the Sanatorium. Practically all of the patients to be presented in this series were diagnosed roentgenologically. The few terminal cases that did not receive the X-ray examination were diagnosed clinically.

The results of this investigation are based upon the study of 1,336 white and 385 negro patients admitted to the Waverley Hills Sanatorium during a five-year period beginning in 1930. Of the 1,336 white patients, 95, or 7 per cent, had minimal pulmonary tuberculosis; 467, or 35 per cent, were moderately advanced, and 774, or 58 per cent, were diagnosed as having far-advanced disease at the time of admission. Only one patient with minimal pulmonary tuberculosis has been diagnosed as having intestinal tuberculosis during the past five years. Of the 467 moderately advanced patients, 31, or 6.6 per cent, were positive for intestinal tuberculosis. One hundred and forty, or 18.1 per cent, of the 774 patients with far-advanced disease were so diagnosed. The percentage of "positive intestines" in the total group of 1,336 white patients was 12.8. The percentage found to have intestinal tuberculosis in the advanced pulmonary group alone was 13.8.

Of the 385 negro patients examined during the past five years, 18.2 per cent were found to be suffering with intestinal tuberculosis. Considering the advanced cases alone, 19.0 per cent were so diagnosed. Only 14, or 3.6 per cent, of these 385 negro patients had minimal pulmonary tuberculosis at the time of admission and none of them had intestinal

[1] From the Waverley Hills Sanatorium, Waverley Hills, Kentucky.

tuberculosis. Ninety-six, or 24.7 per cent, were moderately advanced, and of this number 6, or 6.3 per cent, had "positive intestines." Two hundred and seventy-five, or 71.7 per cent, of the total number examined during the past five years were far advanced. Sixty-four of these, or 23.3 per cent, were diagnosed as having intestinal tuberculosis.

By referring to table 1 it can be seen that 93 per cent of the white and 96.4 per cent of the negro patients during the five-year period had advanced pulmonary tuberculosis at the time of admission to the Sanatorium. The principal difference to be noted in the two races is the considerably higher percentage of far-advanced and smaller percentage of moderately advanced cases in the Negro. Acuteness of onset, together with rapid progression and greater destruction of lung tissue, is not an uncommon occurrence in the negro race. By the time we first have an opportunity to observe them in the Sanatorium, therefore, the majority have progressed to the far-advanced stage, and, by and large, to a more destructive stage than seen in the white race. In a previous communication it was pointed out that the average length of time which elapsed between the first symptom of pulmonary tuberculosis and hospitalization was 10 months for the white and 5½ months for the Negro, and that there was practically no difference in the time-interval for males and females.

This comparative lack of resistance to tuberculosis in the negro race, giving us such a serious pathological picture in such a short interval of time, is no doubt responsible for the high death-rate, as well as the comparatively unfavorable response to collapse therapy referred to in previous communications. It would also appear that these factors would tend to lead to a higher percentage of intestinal tuberculosis in the Negro than is seen in the white. Rapid breaking down of lung tissue would be conducive to larger numbers of tubercle bacilli coming in contact with the intestinal mucosa at more frequent intervals.

In table 1 it is seen that intestinal tuberculosis in the white race was found almost three times more frequently in the far-advanced group than in the moderately advanced group. In the Negro it occurred almost four times more frequently in the far-advanced group. Both white and negro races, on the other hand, had practically the same incidence of intestinal tuberculosis when the pulmonary disease was moderately advanced. It would appear, therefore, that earlier diagnosis in both races, particularly before the disease has reached the far-advanced stage, would give us greater hope than any other factor in reducing the incidence of intestinal tuberculosis. Proper treatment, including collapse therapy, could then be instituted with a large degree of success.

TABLE 1

Patients classified according to the degree of pulmonary disease, showing percentage of intestinal tuberculosis in each classification

	TOTAL	MINIMAL	MODERATELY ADVANCED	FAR ADVANCED
	White			
Intestinal tuberculosis	1,336 172(12.9%)	95(7%) 1(1%)	467(35%) 31(6.6%)	774(58%) 140(18.1%)
	Negro			
Intestinal tuberculosis	385 70(18.2%)	14(3.6%) None	96(24.7%) 6(6.3%)	275(71.7%) 64(23.3%)

TABLE 2

Patients classified according to the degree of pulmonary disease and sex. The percentage of intestinal tuberculosis is given in each classification

	TOTAL		MINIMAL		MODERATELY ADVANCED		FAR ADVANCED	
	Male	Female	Male	Female	Male	Female	Male	Female]
				White				
Intestinal tuberculosis	583 79(13.5%)	753 93(12.3%)	35 None	60 1(1.6%)	181 11(6.1%)	286 20(7.0%)	367 68(18.5%)	407 72(17.7%)
				Negro				
Intestinal tuberculosis	213 38(17.8%)	172 32(18.6%)	6 None	8 None	49 3(6.1%)	47 3(6.4%)	158 35(22.1%)	117 29(24.8%)

Brown and Sampson state that Lisenby (1927) found the greatest incidence of secondary intestinal tuberculosis to occur in colored females, followed in order by white females, colored males and white males. In our own series (table 2) colored females were also in the lead but only when the pulmonary disease was far advanced. Colored males were second in order of incidence, followed by white males and females, who showed about the same incidence.

An attempt was made to determine whether there had been a falling-off in incidence of intestinal tuberculosis during the past five years, and it was also our purpose to compare the incidence in our series, which includes only patients examined since 1930 with other series examined prior to that date. In 1930 and 1931 the average percentage of white patients with far-advanced disease admitted to the Sanatorium was 58.2, and the percentage of intestinal tuberculosis found in the moderately advanced and far-advanced groups combined was 16.5. The average percentage of far-advanced patients admitted during the years 1932, 1933 and 1934 was 57.9, whereas the percentage of intestinal tuberculosis in the advanced pulmonary groups had fallen to 11.9. Thus, there has been a substantial decline in intestinal tuberculosis in the white race during the past five years, even though the percentage of cases with advanced pulmonary tuberculosis has remained the same. We cannot attribute this decline to earlier diagnosis therefore, nor can it be attributed to collapse therapy because the diagnosis of intestinal tuberculosis was made on all of these patients at the time of admission to the Sanatorium and before any form of collapse therapy was instituted.

On the other hand, the percentage of Negroes admitted with far-advanced pulmonary disease in 1930 and 1931 was 74.4. For the years 1932, 1933 and 1934 the percentage was 69.2. The percentage of intestinal tuberculosis for these two periods was 18.4 and 19.3, respectively. From these figures we can certainly conclude that there has been no reduction in the incidence of intestinal tuberculosis in the Negro during the past five years.

In the 1930 edition of their book on *Intestinal Tuberculosis*, Brown and Sampson state that a study of 1,801 routine cases admitted to the Trudeau Sanatorium, which accepts only favorable and usually early cases of pulmonary tuberculosis, showed that 148 were positive for intestinal tuberculosis, of which 4 were minimal, 99 moderately advanced, and 45 far advanced. Of the total number examined, 355 were minimal, 1,100 moderately advanced and 175 far advanced. The percentages of

intestinal tuberculosis in the minimal, moderately advanced and far advanced groups were therefore 1.1, 9.0, and 25.7 per cent, respectively. In the preface to the same edition of this book, the authors state that, of 5,542 patients examined prior to 1930, 1,465 were found to be suffering with intestinal tuberculosis, or a percentage of 26.5. It is assumed that practically all of these patients were white and, comparing this figure with our own 12.9 per cent in table 1, it is quite evident that the incidence of intestinal tuberculosis has declined considerably since 1919, when the roentgenological diagnosis of this condition was placed on a firm foundation by the work of Brown and Sampson at the Trudeau Sanatorium.

CONCLUSIONS

1. The incidence of intestinal tuberculosis is definitely on the decline. This statement is based on the comparison of our percentages obtained since 1930 with those of the Trudeau and Saranac Lake series compiled prior to that date.

2. This decline in incidence, according to our series, cannot be attributed to earlier diagnosis, nor has it been due to collapse therapy, since all of our cases were diagnosed shortly after admission to the sanatorium and before collapse therapy was instituted.

We wish to express to Dr. Lawrason Brown and Dr. Homer L. Sampson our sincere appreciation of their helpful criticism of this paper. We also wish to thank Mr. Chas. E. Murphy for his valuable assistance in the compiling of our statistics.

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THE RÔLE OF NON-ACID-FAST RODS AND GRANULES IN THE DEVELOPMENTAL CYCLE OF THE TUBERCLE BACILLUS[1,2]

MORTON C. KAHN AND JOSÉ F. NONIDEZ

The reproductive mechanism utilized by the tubercle bacillus is a subject of great importance, and is still one about which bacteriologists working in this field are not entirely agreed.

Generally speaking, there are at present three schools of thought. The first may be said to believe that this organism multiplies only by simple fission without any change in staining characteristics. All granule, coccoid and non-acid-fast types being considered degenerative, "involution," or aberrant forms. The second group believes that a more complicated type of reproductive mechanism may be followed which may include a granule and non-acid-fast phase. The third group, represented chiefly by French investigators, and in this country by Mellon (1) (2) (3), describe a filterable phase in the life-cycle of the tubercle bacillus.

The results of an investigation upon this subject were published by Kahn (4) in 1929, and tended with certain modifications to support the opinion that the tubercle bacillus may at times undergo a pleomorphic type of developmental cycle, including a small granule and non-acid-fast phase. For this study the single cell method of approach was employed. Single organisms or small groups of from two to six were isolated in microdroplets of Long's synthetic medium. These microdroplets were small enough, for the most part, to be included within the circumference of the oil-immersion field, and with the method employed were preserved from drying or spreading so that periodical observation could be made on identical individuals as well as on the forms resulting from them for several days or weeks.

While variation did occur, the most usual type of reproductive process observed was the segmenting of the rod into three or more ovoid units,

[1] From the Departments of Public Health and Preventive Medicine and Anatomy, Cornell University Medical College, New York City.

[2] This study is part of a group investigation being carried on in conjunction with the Medical Research Committee of the National Tuberculosis Association.

and the reduction of these units into fine granules from which later extremely fine and delicate rods were found to develop. These small rods elongated and developed with varying rapidity until they became the size and shape of what may be called the mature acid-fast tubercle bacillus. In the fine-granule phase of this developmental cycle, as well as in the case of the small and delicate rods which were observed to evolve from the granules, the organisms appear distinctly non-acid-fast.

The purpose of the present communication is to add new evidence in support of this pleomorphic type of developmental cycle and to discuss some of the contemporary publications pertinent to the subject.

In the following sections, we will attempt to demonstrate that the tiny non-acid-fast granules and rods which one of us observed to be the progenitors of the acid-fast rods in the single-cell preparations of the H37 strain seemingly also play a similar reproductive rôle in the bovine type. Furthermore, as will be seen, these non-acid-fast forms, especially the small granules, are apparently lacking in cultures of certain other types of mycobacteria. It would also appear from our experimental evidence that the above-mentioned non-acid-fast bodies are to be seen not alone in the microdroplet preparations but also in young gross cultures growing upon egg, glycerol-agar medium and upon the liquid synthetic medium of Long. Thus the possible objection that the non-acid-fast bodies are induced to develop because of the artificial conditions assumed to be present in the microdroplet containing the single cell may be removed.

It is true that, when the usual Ziehl-Neelsen stain is applied, these non-acid-fast organisms are not often observed by most workers and, when present, they may be readily mistaken for extraneous material, especially if the slide has a faint blue background. The present study will indicate that this apparent lack of the non-acid-fast forms may be explained on the grounds that it is customary in most laboratories to examine cultures after 3 to 6 weeks' incubation, the time when the non-acid-fast types have diminished considerably. It appeared to us that, if these non-acid-fast elements are as important in the reproduction of the tubercle bacillus as the single cell studies indicated, then one should be able to demonstrate them readily in young macroscopic cultures as well as in the microdroplet preparations. A short preliminary report on the occurrence of these forms in vertical sections made from young colonies has already been published (5). Since that time the work has been greatly extended, and it has been found possible also to demonstrate the non-acid-fast elements in *young* cultures smeared upon slides and stained by the ordinary Ziehl-Neelsen method.

OCCURRENCE OF NON-ACID-FAST RODS AND GRANULES IN VERTICAL SECTIONS OF YOUNG COLONIES

Vertical sections were made of young colonies growing upon Petroff's egg medium, egg-yolk medium not containing dye and of young-growth membrane growing upon Long's synthetic medium. Three different processes were used in the preparation of sections, namely (1) the frozen-section method, (2) the paraffin method, and (3) the combined celloidin-paraffin method.

The frozen section method: Small blocks of the medium with the attached colonies were preserved for 8 hours in 15 per cent formalin neutralized with powdered calcium carbonate. The blocks were rinsed with distilled water and suspended in a 3 per cent solution of warm agar. After cooling a cube was trimmed. The block of agar enclosing the colony was placed upon a drop of distilled water on the stage of the freezing microtome and frozen with liquid CO_2, vertical sections of the colony were cut. The sections were lifted from the edge of the knife with a fine brush and put into sterile distilled water, where they spread; they were transferred to clean slides which had previously been smeared with albumin fixative, spread flat, allowed to dry and stained with the Ziehl-Neelsen method in the usual way, finally being mounted in damar under a cover-glass. This method served as a control for the other methods about to be described, as the colonies are never in contact with a fat solvent, a point of considerable importance in the present work. As a disadvantage, may be mentioned the fact that it is seldom possible to cut sections below 8.0 micra in thickness without disintegration of the colony. But a number of areas are clearly visible even in the thicker sections where the non-acid-fast rods and granules are present in great profusion.

The paraffin method: Small blocks of the medium with the attached colonies or particles of the growth membrane were fixed in 95 per cent alcohol for 24 hours, dehydrated with absolute alcohol and cleared with xylol. In most cases, an intermediate mixture of equal parts of absolute alcohol and xylol was used before the blocks or particles were put in pure xylol. Small colonies are usually quite clear in 4 to 6 hours, but in some cases they were left in xylol longer. Hard paraffin, having a melting point of 56 to 58°C., was employed for embedding. Serial sections, 3 to 5 micra thick, were cut with the rotary microtome. The sections were fixed to the slide with a minimum amount of albumin-glycerine mixture and spread in a drop of distilled water placed on the slide. After they were thoroughly dried, the paraffin was dissolved with xylol and the

sections rinsed once more with pure xylol to remove every vestige of paraffin. After this the slide was flooded with absolute alcohol to remove any trace of the paraffin solvent. Staining was accomplished with the Ziehl-Neelsen method and, after drying, they were covered with a drop of damar and a cover-glass added.

The combined colloidin-paraffin method: While the preceding method was applied successfully to the study of colonies of the human and bovine tubercle bacillus, it was found that it could not be as successfully applied with other bacterial colonies such as the avian tubercle bacillus, especially the S mutant, as the colonies of this species became detached from the medium after they had been in the alcohol for a short while; and, in view of the minute size of these structures, especially in young cultures, they were extremely difficult if not impossible to handle during the subsequent staining and mounting processes. To overcome this difficulty a method was devised whereby the colonies could be cut *in situ*, that is, attached to the egg medium.

The blocks of medium with the attached colonies were fixed in a solution of celloidin in equal parts of absolute alcohol and ether. The solution must have a syrupy consistency and should be changed after a few hours, since water extracted from the colony and egg medium causes it to become cloudy due to hydration of the absolute alcohol. The length of fixation was from 24 to 48 hours.

The blocks were seized with forceps and dropped into chloroform which causes a sudden hardening of the film of celloidin surrounding the colony. The latter is thus solidly held in place. The blocks must be left in the chloroform at least 10 hours to bring about thorough penetration. Since chloroform is a paraffin solvent, there is no need to employ other clearing agents.

From the pure chloroform the blocks are placed in a solution of paraffin in chloroform and kept overnight at a temperature of 38–40°C. They are then transferred to melted paraffin (56°–58°) for four or five hours, changed two or three times, and embedded. Thin sections, some 3 to 6 micra, can be cut; they are fixed to the slide with albumin glycerine, dried, and the paraffin dissolved with xylol. From xylol, the slides are placed, 10 to 15 minutes in absolute alcohol, in which the celloidin is dissolved. They were stained with the Ziehl-Neelsen method. The advantages of the combined method in cases of crumbly material (old-growth membrane) or colonies not firmly attached to the culture medium are obvious.

Criticism of method, fat solvents, etc.: The non-acid fast rod and granule forms, which will be described subsequently, appeared in both the young colonies treated with alcohol and xylol, as well as in the sections which were cut with the freezing microtome, where accordingly no fat solvent was employed. The presence of these forms cannot, therefore, be attributed to the uneven dissolution of the fatty substance by the reagents mentioned above. However, as this point is that upon which the entire experiment may be said to lean, further experiments were designed to determine whether the reagents employed could in any way interfere with the results. In the first place, if alcohol and xylol do influence the staining capacity of *M. tuberculosis*, this organism would seldom have been seen in its acid-fast conditions in sections of tuberculous tissue when prepared with the ordinary histopathological method, for the organisms often occur in small numbers and are usually scattered. Unless the penetration by xylol be thorough, it would be impossible to cut sections of such material. Also, in a study already reported by us (6) concerning the infection of tadpoles by a cold-blooded strain of *M. tuberculosis*, large numbers of tadpoles were fixed and sectioned, using the reagents mentioned without in the least affecting the acid-fastness of the strain of organism employed.

As a further control, a number of smears were made from growing colonies of *M. tuberculosis*, human, bovine and avian. Some of these slides were stained with the Ziehl-Neelsen method immediately, while others were placed in a mixture of equal parts of absolute alcohol and xylol for 24 hours. They were thoroughly rinsed with absolute alcohol, allowed to dry, and then stained with the aforementioned technique. No relative increase of non-acid-fast to acid-fast organisms occurred. From our results, it would seem that, although the microörganisms were thinly scattered over the slide, 24 hours in these reagents did not influence their subsequent staining.

As subsequent descriptions will indicate, the sectioned young colonies for the most part revealed definite zones of stratification, the peripheral stratum being composed principally of tiny non-acid-fast granules and exceedingly small and delicate non-acid-fast rods. The core or medulla of these young colonies were found to be populated principally by relatively large acid-fast rods with relatively fewer of the non-acid-fast elements. On this account, it may be inferred that the peripheral non-acid-fast zone is an artifact, brought about by being exposed to the fixing agents for a longer period, these agents penetrating more slowly to

the depths of the colony, and, therefore, not acting in that locality as long. That this is not the case will be shown by the fact that young and small colonies were the ones which revealed the most definite stratification. Older and considerably larger colonies which had ceased their growth revealed little if any such structures. If the first possibility were a matter of fact, one would expect some penetration in the old colonies and a zone of the non-acid-fast elements in these as well. Furthermore, while the tiny non-acid-fast rods and granules are most abundant in the peripheral zones of the young colonies, and least abundant in the core or medulla, as a matter of fact both kinds are scattered throughout the entire colony, as presumably there is some growth taking place in the entire area.

Also, as will be shown, other types of non-acid-fast bacteria yield relatively few non-acid-fast bacillary forms and none of the tiny granule types which are conspicuous in the human and bovine strains. An illustration in this regard is the *M. marinum* isolated from an iguana by Aronson. Bacteria in sections of these colonies invariably appeared for the most part strongly acid-fast.

In the study recently reported by us, this strain of mycobacterium was fed to tadpoles and tuberculosis was induced with the production of tubercles. These preparations had four separate applications of xylol, one of 20 hours, one of from 6 to 8 hours at 40°C. The sections were cleared with xylol and the paraffin dissolved off with the same chemical. Few, if any, non-acid-fast forms were encountered in these sections.

As concerns the use of albumin for fixing the sections to the slides, this substance is a mixture of equal parts of the whites of fresh eggs and glycerine. It is carefully filtered after preparation. When spread thin upon a clean slide, it does not take the stain; hence its current use in histology. In order to make sure that no background could result from the use of this mixture in any way simulating microörganisms, and that the paraffin used for embedding did not leave a confusing residue, paraffin sections *not* containing the colony were fixed to slides smeared with the albumin-glycerine. After the paraffin was dissolved with xylol and the slides rinsed with absolute alcohol, the Ziehl-Neelsen stain was applied. Nothing resembling rods or granules could be seen in these preparations, the background being entirely colorless.

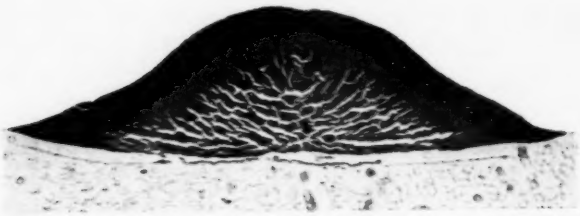
We feel therefore, that these non-acid-fast tubercle bacilli are not in the nature of an artifact due to a misinterpretation of technique, but are an integral part of the developmental cycle of certain mycobacteria, at least under our experimental conditions.

VERTICAL SECTIONS OF HUMAN MYCOBACTERIUM TUBERCULOSIS COLONIES

For the purpose of this experiment, three cultures of the H37 Saranac Laboratory strain were employed and were obtained from separate sources. One of these was the offspring of the single-cell plant made by one of us (Kahn) in 1927, the other was obtained from Dr. S. A. Petroff of the Trudeau Laboratory, while the third was obtained from Dr. Kenneth Smithburn of the Rockefeller Institute. These were undissociated strains and were kept viable upon Petroff's egg-medium slants. Employing the usual filtering technique of Petroff, widely separate colonies were obtained of these three cultures upon petri plates containing the same medium. Small blocks of the medium with the attached colony were cut from the plate and one of each of these was sectioned by the methods already described. As the results obtained were identical in the case of these three cultures with these methods, they may be described as a unit.

Colonies appear on the plates of pin-head size in from three to four weeks. These, after sectioning, measure from 0.75 to 0.5 mm. in length and about 0.5 mm. or less in depth after staining by the Ziehl-Neelsen method. When these young colonies are examined under the low power of the microscope, two definite zones of stratification are revealed, the peripheral zone appearing distinctly blue in color, while the remainder of the colony appears acid-fast. In colonies of this age, the blue area extends to about one-half of the depth of the colony and on occasion has been observed to occupy almost the entire area save a narrow zone toward the bottom. If the blue area is examined under the oil-immersion lens, it will be found to be composed principally of myriads of exceedingly small non-acid-fast granules and non-acid-fast rods. Some of these forms measure from about 0.2 to 0.84 micra, while many are too small to measure with any degree of accuracy. Although the impression gained from examination under the low power is one of uniform blueness, when the higher magnifications are employed, small acid-fast rods and coccoid bodies may be found scattered among the cyanophilic elements, although in this area the acid-fast forms are greatly outnumbered. The extreme outer edge of these young colonies was found to be composed exclusively of non-acid-fast granules and rods. At times the growth appears so compact that the individual forms are only discernible in the cracks and crevices which appear. However, if a little pressure is applied to the cover-slip, the sections will be crushed in parts and the non-acid-fast granules and rods may be seen without difficulty.

The more circumscribed remaining area, which for the most part holds



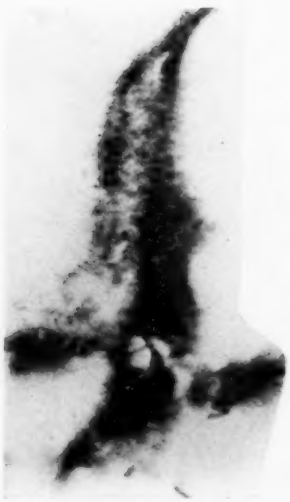


PLATE 1

The top figure of the plate is a photomicrograph, taken in color, of a vertical section through an *M. tuberculosis* colony after Ziehl-Neelsen staining (× 200). The peripheral zone, which shows the myriads of non-acid-fast granules and rods, may be seen in contrast to the lower stratum or medulla, which is composed principally of strongly acid-fast rods.

The lower figure is a photomicrograph, taken in color, of a vertical section through a young growth membrane of *M. tuberculosis* after Ziehl-Neelsen staining (× 300). The large numbers of non-acid-fast forms may be seen, while here and there acid-fast organisms occur.

the carbol-fuchsin stain, was found to be composed principally of acid-fast rods of varying length, although in the case of these young colonies a relatively considerable number of the small non-acid-fast forms are also to be found in this locality.

At the extreme bottom edge, where the colony comes in contact with the medium, the small non-acid-fast bodies are found in about equal numbers with the acid-fast forms.

In the case of human colonies from five to seven weeks of age, which were grown, sectioned and stained in the same manner, the picture obtained is quite striking. Here the inner acid-fast zone is more extended comprising about two-thirds or four-fifths of the entire colony (see figure 1). The remaining peripheral zone may be divided into two parts, the outermost of which appears definitely non-acid-fast. Directly under this there is a narrow but distinct area which appears as a stratum of paler color. When an examination is made under oil-immersion magnification, the outer peripheral zone which appears blue on examination under the low power is found to be composed of vast numbers of non-acid-fast granules and rods. These blue elements are of the same size as already described in the younger colonies. Beside these, however, and also in the same peripheral zone, are to be found a considerable number of acid-fast rods which contain the deep-staining intracellular dark appearing areas. The lower stratum, which is strongly acid-fast, is composed principally of large definitely acid-fast rods and coccoid bodies with small non-acid-fast rods and granules scattered through the cracks and crevices which appear in this portion of the colony. The somewhat lighter staining central stratum is composed of acid-fast rods and coccoid bodies, although relatively a considerable number of the non-acid-fast forms are also encountered in this locality. The cracking of the acid-fast core of colonies of this age may be an artifact due to drying prior to Ziehl-Neelsen staining. However, when silver nitrate is used for impregnation and the colonies are not allowed to dry, a number of well-defined vacuoles is present in this strongly acid-fast "medulla," which, as will be discussed later, gives additional evidence that this portion of the colony is the oldest, for these vacuoles do not appear in the peripheral zone composed chiefly of the non-acid-fast forms nor in young colonies.

VERTICAL SECTIONS OF YOUNG- AND OLD-GROWTH MEMBRANE TAKEN FROM LONG'S LIQUID MEDIUM

By planting minute flecks of the chalk-white young membrane from the H37 strain, and then replanting from the edges of this inoculum as

soon as growth is apparent, the culture may be spurred to rapid and vigorous growth if this procedure is repeated often. Perceptible growth may be obtained in 4 days.

Membranes from 7 to 14 days of age were sectioned by the aforementioned processes, and revealed vast numbers of the small non-acid-fast granules and rods intermingled with acid-fast rods and coccoid bodies. In certain areas of these specimens a considerable number of large strongly acid-fast rods was also encountered, sometimes without any acid-fast elements. It is possible that these zones may be that area of the membrane which is adjacent to the older growth in the flask.

The flasks from which these specimens were obtained were then allowed to incubate at 37°C. As is well known, this young white growth, as time goes on, becomes yellowish brown in color and wrinkled. After a lapse of 10 weeks, these membranes were again sectioned. Few, if any, non-acid-fast forms were encountered. The impression was gained of principally large strongly acid-fast organisms. A similar experiment was performed by Bezançon and Philibert (7). These observers obtained growth membrane from glycerine-boullion cultures. This was washed in absolute alcohol and imbedded in paraffin. Sections were then cut and stained with the Ziehl-Neelsen or Fonte's stain. In very young cultures only a network of non-acid-fast material was seen. After 16 to 25 days, acid-fast rods were in evidence. These writers extended their observations to several different cultures of tubercle bacilli, and came to the conclusion that the acid-fast rod is only a temporary phase in the developmental cycle.

DEMONSTRATION OF NON-ACID-FAST RODS AND GRANULES IN YOUNG CULTURES BY THE STANDARD ZIEHL-NEELSEN STAIN

At the outset, in order to avoid confusion, it may be well to describe briefly the technique of staining as conducted in our laboratory. After the carbol-fuchsin is applied, the slide is gently steamed for exactly five minutes. This stain is washed off with distilled water. The acid-alcohol mixture is then applied and poured from the slide immediately. It is then reapplied and allowed to remain in contact for one minute. After washing with distilled water, the slide is stained with methylene-blue for one minute and washed in distilled water again.

The specimens to be stained are allowed to become almost dry upon the slide and are then gently rubbed into a *pasty consistency* with a *platinum spatula*, to insure even distribution. After drying in air, the organisms

are fixed by one rapid passage above the flame. Unless this procedure is resorted to the non-acid-fast forms are not demonstrable in the young material.

The cultures employed for this experiment were induced to rapid growth by several successive transplants on Long's liquid medium. When the young white membrane had increased in size the edges were carefully removed with a platinum loop and seeded upon the surface of a fresh flask of medium. After a number of transfers made in this fashion, visible growth may be discerned in 4 days. Several Erlenmeyer flasks of 100- to 200-cc. capacity were seeded simultaneously with the four-day-old growth membrane. These flasks were filled with the medium in such a fashion as to present the largest possible surface. Only two observations were made on any one flask, in order to avoid contamination with air organisms attendant upon frequent opening and closing of the same flask. Growth seemed to be relative in all of the flasks.

Periodic stains were then made on slide preparations made from these membranes varying in age from 4 to 145 days. It was found by actual count that, in the membranes 4 days of age, the bacterial population was composed of about 90 per cent tiny non-acid-fast rods and granules and about 10 per cent acid-fast rods and coccoid bodies. From the seventh until the 41st day, the percentage of non-acid-fast forms fluctuated greatly, at times revealing 80 per cent and at other times comprising as low as 5 per cent of the bacterial population. A considerable portion of this fluctuation is unquestionably due to errors in taking the sample, as new, chalk-white young membrane is being continuously formed and interspaced with the older corrugated cream-colored growth. Nevertheless, these counts serve to reveal the fact that the non-acid-fast are most abundant and conspicuous while the culture is actively growing. After 41 days there occurred a precipitous drop in the cyanophilic elements, and after 56 days their numbers did not exceed 7 or 8 per cent, while at the end of 115 days the culture was composed almost entirely of large acid-fast forms. The cultures were observed for 145 days and, although the membranes had sunk to the bottom of the flasks, there was no further evidence of increase in the numbers of non-acid-fast forms. This experiment tends to confirm the results obtained by Alexander (8), who made daily stains of material obtained from lightly seeded plates of Bordet and Gengou medium. She employed two recently isolated human strains as well as R and S dissociants of the avian tubercle bacillus. It is of interest to note that the results obtained after five days are comparable

to ours, for after that time only non-acid-fast cocci and diplococci appeared on the smears. No acid-fast organisms were observed. Smears prepared from 2½- to 4½-weeks-old cultures revealed an abundance of both acid-fast and non-acid-fast types.

VERTICAL SECTIONS OF OLD COLONIES OF HUMAN MYCOBACTERIUM TUBERCULOSIS

To serve as controls, sections of old colonies were also prepared by the aforementioned methods. These, as far as could be determined, had ceased their growth. The colonies used for this purpose varied in age from 10 to 14 weeks. Examination of the Ziehl-Neelsen-stained sections under the low power failed to reveal the zones of stratification noticed in the young colonies, while the oil-immersion magnification brought to view a bacterial population composed almost exclusively of strongly acid-fast rods. A few non-acid-fast organisms were encountered here and there at the extreme peripheral edge and also in that portion of the colony which was in close contact with the egg medium. Sections of these old colonies were then crushed between the slide and cover-slip to bring to view any non-acid-fast forms which may have escaped notice. Such treatment did not reveal any additional non-acid-fast rods or granules, and the impression was gained that these old colonies are composed almost exclusively of acid-fast rods.

VERTICAL SECTIONS OF YOUNG AND OLD COLONIES OF BOVINE STRAINS OF MYCOBACTERIUM TUBERCULOSIS

For the purpose of this experiment, three strains of bovine tubercle bacilli were employed. One of these was an undissociated B1 strain obtained from Dr. S. A. Petroff. This culture was received upon Petroff's egg medium and the colonies desired for sectioning were grown upon plates of the same medium.

The second culture was composed principally of smooth-appearing colonies obtained from the B1 strain and kindly given to us by Dr. Kenneth Smithburn. The original culture obtained from Dr. Smithburn was on egg-yolk medium not containing any dye. As long as the organisms remained upon this medium they continued to give rise to the characteristic "S"-appearing colonies. When transferred to other types of medium, however, these smooth characteristics were lost, and the colonies obtained resembled those of the undissociated B1 culture. For purposes of sectioning, the colonies were grown upon the egg-yolk medium from parent cultures which had been kept upon the same substance.

A third culture, the Ravanel strain of the bovine organism, was kindly supplied by Dr. Jules Freund of this institution. This culture was upon glycerol-agar and the colonies employed for sectioning were grown upon the same substance.

In the case of the undissociated B1 strain, and also the "smooth" type of colony from this strain, colonies large enough to section were obtained in from three to five weeks. Growth upon glycerol-agar was somewhat slower; therefore, the colonies from the Ravanel culture were not sectioned until after some 6 weeks after seeding.

In the case of all three cultures, the results obtained were the same as with the H37 strain. One observes the peripheral zone composed of vast numbers of minute non-acid-fast granules and rods, with acid-fast organisms scattered here and there. The medulla is composed of strongly acid-fast bacteria with the non-acid-fast types interspersed among them. Sections were then made of colonies from these strains varying in age from 14 to 18 weeks; only occasional non-acid-fast types were encountered, the impression being gained that their numbers were far less than 1 per cent of the acid-fast population. In view of the similarity of these findings with those obtained for the H37 strain, a detailed description of the bovine colony sections is not necessary.

VERTICAL SECTIONS OF AVIAN MYCOBACTERIUM TUBERCULOSIS COLONIES

The A1 strain of the avian tubercle bacillus was employed for this experiment. The R and S types were obtained originally from Dr. Petroff and subjected to single-cell isolation and reported on in 1933 (9).

These strains were kept going upon Petroff's egg medium, and colonies from which the sections were prepared were obtained from petri plates containing the same substance.

In the first experiment, colonies 4 weeks of age were employed. Examination under the low power of the microscope did not reveal the zones of stratification as was the case with the human and bovine strains. The impression gained at this magnification was one of acid-fastness throughout. Under oil-immersion magnification, however, numerous non-acid-fast large and small rods were encountered scattered at the periphery of the colony, but there was a great majority of acid-fast rods of similar size and shape. Extending into the field like papillae from the extreme peripheral edge of the colony, were to be observed rows of non-acid-fast rods. In both the R and S avian colonies of this age, the non-acid-fast granules which are conspicuous in the human- and bovine-colony sections were not to be observed.

It was considered that the colonies employed were too old to yield these forms, but it is difficult to obtain younger colonies on the medium employed. If, on the other hand, streaks are made across the plate, using a fairly heavy inoculum, growth may be obtained in about 2 weeks. Blocks of medium containing a portion of this streak-culture were cut from the plate and sectioned after the manner employed for the colonies. Growth of this age, however, did not reveal the presence of the non-acid-fast granules, and the non-acid-fast rods observed were not much smaller than, nor different from, the acid-fast bacteria. The fringe of blue-staining organisms at the extreme outer edge was thicker and more pronounced and conspicuous in the sections made from streak-cultures of this age.

In the case of sections obtained from the "S" colonies and streak-cultures, certain spots staining intensely blue were to be observed here and there. These were mashed by applying pressure and also dissected out with microneedles. The impression is gained that this substance is in the nature of amorphous mucoid material. Sections of avian R and S colonies, varying in age from five to eight weeks, revealed very few non-acid-fast bacteria.

VERTICAL SECTIONS OF COLONIES OF MYCOBACTERIUM SMEGMATIS, MYCOBACTERIUM MARINUM (IGUANA), MYCOBACTERIUM OF "RAT LEPROSY" (CHAPIN) AND MYCOBACTERIUM PHLEI

The sections made from colonies of the above mentioned organisms varied in age from 5 to 19 days. Those of *M. smegmatis* and *M. rat leprosy* gave the same impression; that is, there seemed to be no zones of stratification nor could any non-acid-fast granular or coccoid bodies be demonstrated. These colonies seemed to be composed entirely of relatively long acid-fast rods with not a few non-acid-fast rods of about the same nature scattered here and there. In the young colonies there were considerable numbers of non-acid-fast rods at the peripheral zone, but a modicum of the acid-fast rods was also present at that locality.

The colonies of *M. marinum* (iguana) revealed somewhat the same picture save that the non-acid-fast rods seemed to be distinctly fewer.

As regards the sections of *M. phlei* colonies, an entirely different picture is presented. The young colonies show myriads of acid-fast and non-acid-fast coccoid bodies and also large numbers of acid-fast and non-acid-fast rods. The rods exhibit various degrees of pleomorphism, regardless of their tinctorial characteristics. Toward the peripheral zones of these

colonies, the non-acid-fast elements are distinctly more numerous. The zones of stratifications in the colonies of this microörganism, while not as distinct as in the case of the human or bovine tubercle bacilli, are more clear-cut than those of the other members of the mycobacteria which were observed by us.

FILTERABILITY

Our description of the small granule phase in the developmental cycle of the tubercle bacillus has been interpreted by numerous workers as additional evidence that this organism may during its growth-process undergo a filterable phase. In Gay's recent book (10), Steinbach states

> Very conclusive evidence of a filterable stage of the tubercle bacillus has been brought forth by Kahn, who studied the life cycle of the tubercle bacillus by observing the changes in the division of a single cell. Steinbach goes on to outline the changes which were observed. In the article to which this writer draws attention (4), it was stated as follows—"It is possible that some of these individuals may be small enough to be ultramicroscopic, and it is conceivable also that in this stage of its development the bacillus of the tuberculosis may be a filter passer although experiments of ours have not been concluded to prove this point."

It is, therefore, pertinent at this time to record the results of a series of experiments which were undertaken by one of us (Kahn), with the aid of Mrs. Eric Schwarzkopf. The H37 strain of human tubercle bacillus, also an undissociated strain of the B1 bovine organism, were employed for these experiments. The ages of the cultures varied from one week to four weeks and were grown upon Long's synthetic liquid medium. The growth membranes were removed from the liquid under sterile precautions and carefully triturated in a sterile mortar. Sufficient sterile distilled water (pH 7.0) was added to bring this mixture to a milky consistency. After removal from the mortar, enough sterile distilled water was added to bring the suspension of bacteria to a density of about 2 billion per cubic centimetre. Filtration was then undertaken with new and tested Berkefeld filters of the N, V and W grade, as well as with the supposedly neutrally charged membrane filters of Zsigmondy-Bachman having varying pore volume. Three cubic centimetres of every filtrate were injected intraperitoneally into each of 5 guinea pigs and liberal amounts of the same filtrate were seeded upon Petroff's medium, glycerol-agar, Long's liquid medium and the medium of Loewenstein. By con-

sulting table 1, it will be seen that the filtrates obtained from the Berkefeld filters appeared to be sterile both on culture and animal inoculation. As regards the membrane filters, four of the 5 guinea pigs receiving the filtrate from the filter having a pore volume from 0.5 to 0.1 micra developed tuberculosis, although growth occurred on the medium in one

TABLE 1

Experiment on the filterability of human and bovine M. tuberculosis

STRAIN	FILTER EMPLOYED	AMOUNT FILTRATE INJECTED INTO EACH GUINEA PIG	NUMBER OF GUINEA PIGS EMPLOYED	RESULT	GROWTH OF TUBERCLE BACILLI WHEN FILTRATE INOCULATED ON FOLLOWING MEDIA			
					Petroff	Long	Loewenstein	Glycerol-Agar
		cc.						
H37	Berkefeld-N	3	5	No tb.	Negative	Negative	Negative	Negative
H37	Berkefeld-V	3	5	No tb.	Negative	Negative	Negative	Negative
H37	Berkefeld-W	3	5	No tb.	Negative	Negative	Negative	Negative
B1	Berkefeld-N	3	5	No tb.	Negative	Negative	Negative	Negative
B1	Berkefeld-V	3	5	No tb.	Negative	Negative	Negative	Negative
B1	Berkefeld-W	3	5	No tb.	Negative	Negative	Negative	Negative
	Zsigmondy-Bachman membrane filters							
	PORE VOLUME							
		cc.						
H37	0.5 to 0.1μ	3	5	Tb. 1 guinea pig	Negative	Negative	Positive	Negative
H37	100 to 50$\mu\mu$	3	5	No tb.	Negative	Negative	Negative	Negative
H37	50 to 20$\mu\mu$	3	5	No tb.	Negative	Negative	Negative	Negative
B1	0.5 to 0.1μ	3	5	Tb. 3 guinea pigs	Negative	Negative	Negative	Negative
B1	100 to 50$\mu\mu$	3	5	No tb.	Negative	Negative	Negative	Negative
B1	50 to 20$\mu\mu$	3	5	No tb.	Negative	Negative	Negative	Negative

Control: Guinea pigs receiving 1 cc. of bacterial suspension prior to filtration developed generalized tuberculosis.

instance only. The filters having a pore volume of less than 0.1 micron appeared sterile and did not give rise to tuberculosis in guinea pigs. All surviving guinea pigs were kept for a period of eight months, and the organs of those which perished were cultured for the tubercle bacillus, as well as the organs of those which were killed at the end of the eight-month interval.

It is to be remembered that the fluid portion of the culture in which the tubercle bacillus had grown was not included in these filtration experiments, except possibly that small amount which adhered to the growth-membrane as it was being removed from its original flask. Therefore, the wasting illness of guinea pigs, which Pinner (11) produced when the actual liquid portion of the culture was filtered and injected, was not encountered. It will be remembered that Pinner was able to produce the same disease with the filtrate after it was heated to 70°C., and that he therefore considers the pathogenic substance not in the nature of a living entity.

During the course of our experiment on filterability, it was observed that an occasional flask of Long's medium into which the filtrate had been seeded became clouded after several weeks of incubation, and three times colonies appeared on solid medium upon which filtrate was inoculated. The clouding of the liquid medium and growth upon solid medium was found to be due to members of the diphtheroid group not pathogenic for guinea pigs. These cultures, besides producing non-acid-fast coccoid types, small and large, also give rise to rods which often contain a considerable amount of acid-fast material, especially when grown on medium designed to support the tubercle bacillus. These organisms are also capable of developing on more simple types of media, such as blood-agar nutrient broth, etc. They may occur as cocci, diplococci, short chains and diphtheroids. These forms appear to us to be strikingly similar to those described by Mellon and his coworkers in the publication already referred to. In our opinion, such forms are contaminating air diphtheroids having by purpose been isolated from the air in two separate laboratories. That they are concerned in the developmental cycle of the tubercle bacillus is indeed highly questionable.

In 1932, F. R. Miller (12) claimed to have induced non-acid-fast coccoid, diplococcoid, rod and diphtheroid forms of the tubercle bacillus to develop by exposing various cultures to a carefully filtered sterile extract which he obtained from a chromogenic variant of the H37 strain described by him (13). For the purpose of his experiment, the extract was added to cultures of the various mycobacteria grown on Petroff's media. In several experiments, Miller states it was necessary to reapply the extract to the cultures two or three times before the characteristic changes were noted. As this experiment has a direct bearing on the problem in which we are interested, Miller's experiment was repeated in this laboratory with the cultures obtained from him through the courtesy of Dr. Florence

Sabin. These cultures were found to be uncontaminated, and the extract from the chromogenic strain was readily prepared in a sterile condition by filtration through the Berkefeld-N candle. When this extract was applied to petri dishes containing cultures on Petroff's medium, the forms described by Miller were sometimes encountered; when however, the experiment was performed using cultures growing in *test-tubes* the types of Miller did not develop. One must infer from this that the larger surface presented by the petri plate, combined with the necessity of opening the dish two or three times at intervals to add the extract, causes contamination by these air diphtheroids to be a more or less frequent occurrence. The question of the filterability of the tubercle bacillus is a vast one, involving a number of factors, and the literature which has developed about the subject is far too voluminous to be reviewed here. The fact remains, however, that before positive results are claimed in this direction adequate attention must be given to the possibility of contamination with these air diphtheroids.

As Cooper (14) points out in his recent article, most investigators agree that a number of serial inoculations are essential before growth from filtrate is obtained. It is obvious that each added manipulation of the culture produces an added hazard of contamination. Furthermore, other observers claim that viable forms are obtained from the filtrate only after lengthy storage at room temperature. It is common knowledge that adequate precaution must be taken if these liquids are to remain free from contaminants after prolonged storage. Furthermore, the first growth obtained by many investigators on a variety of bacteria is disconcertingly similar to the coccoid and diplococcoid phases of the air diphtheroid.

Although it is fully realized that the process of filtration is far from a simple straining or sieving, still our results would indicate that forms smaller than 0.1 micron, if they do exist in our cultures and penetrate the membrane filter, do not grow upon medium nor give rise to tuberculosis in guinea pigs.

We do not agree with Cooper's statement that the presence or absence of single granules in cultures depends chiefly on staining technique, as we have demonstrated that when a young and an old culture are stained upon the same slide the former will show numerous granules, while the latter reveals very few.

DISCUSSION AND SUMMARY

In studying the stained vertical sections of the human and bovine tubercle-bacillus colonies in which the minute non-acid-fast granules and non-acid-fast rods are so conspicuous in certain zones, the question at once presents itself as to which is the older portion of the colony,—the peripheral areas where these forms are abundant or the lower stratum where their place is largely taken by the strongly acid-fast rods. We feel that the peripheral zones are the younger portions of the colony and the zones of active growth for the following reasons: *1:* When vertical sections are made through young colonies of human or bovine strains these non-acid-fast small forms are very abundant in the peripheral areas. While in vertical sections of old colonies which have ceased their growth, the peripheral zone is almost entirely obliterated, there being only a few non-acid-fast forms scattered here and there at the extreme outer edge of the colony, the remaining areas are populated by strongly acid-fast rods. *2:* Vertical sections, made through young- and old-growth membrane taken from Long's liquid medium, reveals the same condition, namely, the young thin white growth membrane exhibits vast numbers of non-acid-fast granules and rods, while the yellow crusty folded old membrane gives rise to relatively few of the non-acid-fast types. Also, periodical Ziehl-Neelsen stains made upon young- and old-growth membrane show the same conditions to obtain, namely, the abundance of the non-acid-fast types in the membranes from four to seven days of age, and their disappearance largely after the 56th day. *3:* The mycobacteria at the periphery of the colony are presumably receiving the most oxygen and the exact requirements of these organisms in this regard is well known. *4:* The single-cell studies on the developmental cycle of the human tubercle bacillus, reported by one of us, indicated these non-acid-fast granules and rods to be the youngest form of this strain. The information obtained from this study of the vertical sections of the human and bovine colonies would seem to substantiate this claim. It seems as though we must consider the colony as a half-sphere; and presumably some growth is taking place throughout the entire area, as evidenced by the few non-acid-fast rods and granules which may be seen scattered here and there through the strongly acid-fast medulla. The peripheral zones reveal considerably larger numbers of these non-acid fast forms, and are, therefore, quite probably the zone of rapid multiplication.

Others who have recently made observations which enable them to

concur in the opinions herein expressed, relative to the rôle of the non-acid-fast rods and granules, as well as the acid-fast coccoid bodies in the developmental cycle of the tubercle bacillus, are Janic (15), Weissfeiler (16), Lominsky (17), Groh (18), Brauer (19) and Alexander (8). In their recent article on the dissociation of the tubercle bacillus, Steenken, Oatway and Petroff (20) state, regarding the R form of the H37 strain, "Granules of various sizes are present in very young cultures. Many non-acid-fast organisms are present in young cultures, but, as they become older, they gradually regain their acid-fast properties."

Others feel that the non-acid-fast forms, as well as the acid-fast coccoid bodies, are fragments of dead or degenerating bacilli. Among these are Oerskov (21), Gardner (22), and Mayer (23). Seiffert (24) found such forms in culture, but believes their presence due to a disturbed metabolism taking place. Recently, Wyckoff (25) (26) and Wyckoff and Smithburn (27) have published the results of motion-picture studies on the growth of several varieties of microörganisms including *M. phlei*. It was their conclusion that the coccoid bodies, which they noticed, were formed as a result of ageing, elongating again if fresh medium was supplied but otherwise incapable of growth. In their opinion therefore, there was no evidence of what they term a "truly cyclic phenomena." These writers specifically limit their interpretations to the organisms with which they worked and under their own experimental conditions. Nevertheless, other investigators have utilized these findings to show that the coccoid and granule forms of the human and bovine tubercle bacillus are nonviable. In the first place, we have not been able to demonstrate the coccoid forms and granules in vertical sections made from young colonies of *M. marinum*, *M. smegmatis*, *M. rat leprosy* (Chapin), nor in sections made from the avian colonies. Nevertheless, in young colonies of *M. phlei* these forms occur abundantly. If the coccoid and granule forms were in reality the result of ageing as far as the human and bovine tubercle bacilli are concerned, then one would expect old colonies which have ceased their growth to be composed principally of such elements, or at least to show an abundance of them. This, however, is far from the case, the old colonies revealing practically only large strongly acid-fast rods. It is the young cultures only which exhibit the coccoid and granule types. Furthermore, that the formation of these small forms is apparently the function of the economy of rapid growth in certain other types of bacteria, and not of ageing, will be adequately illustrated in a forthcoming publication having to do with motion pictures of the development

of a single cell alone in a microdroplet of medium in which each step may be adequately followed without fear of intrusion from other organisms growing into the field. In the case of certain bacteria, the cleaving of the rod into these minute coccoid bodies begins at once, some of these later elongating into large rods in the same microdroplet of liquid medium which contained the single cell. On a coarser scale this is quite similar to what has been observed for the tubercle bacillus.

We do not feel that there is anything mysterious about the developmental cycle which we have observed; it appears to be a type of segmentation rather than direct fission in which the rate of segmentation surpasses the ability of the elements thus formed to elongate. The bodies become increasingly numerous as they become smaller. The loss of acid-fastness, when the tubercle bacillus is in the granule phase and small-rod phase, may possibly be explained on a metabolic basis. As an example, during the division and resubdivision of the various particles, the potential of elongation does not keep pace with the potential of division. Consequently, there is at certain stages seemingly insufficient time for the organisms to metabolize the substances essential for their acid-fastness. When the potential of division becomes less it is conceivable that the individual granule has more opportunity for growth or elongation, and also for the opportunity of metabolizing the chemicals necessary to acid-fastness.

Whether or not such a process should be termed a life-cycle (developmental cycle, growth-cycle) is, it would seem, merely a matter of the juggling of words, as Winslow (28) has so ably pointed out in his recent article on the subject. It would appear that the departure from the usual orthodox conception in size and staining properties which the tubercle bacillus exhibits in certain phases of its growth, only to return again to the acid-fast rod, would be in the nature of a cyclic phenomenon, and therefore, should be termed a life-cycle, but that the coccoid forms which result from the cleavage of the rod, and the granules which occur from the division of the coccoid forms are thus elaborated by ordinary fission, there is no question.

We do not desire to claim that this is the only means of reproduction afforded the tubercle bacillus. Others may take place and direct fission in the usual sense of the word may well be one of these. It is conceivable, however, that the cycle already described takes place when conditions are favorable.

We were unable to gather evidence which would indicate that the

small granules and rods observed are filterable in the usual sense of the word.

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THE TREATMENT OF TUBERCULOSIS OF THE SKIN BY HEAT

A Preliminary Report[1]

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A perusal of the literature on the therapy of skin tuberculosis indicates the absence of adequate and satisfactory treatment of this disease. This is mainly due to, first, inability to demonstrate the primary focus of infection; second, difficulty in treatment of focus if found; third, inadequacy of therapeutic procedures in the treatment of skin lesions present; fourth, indefinite knowledge of the exact mechanism which produces the various types of lesions.

The treatments used by competent authorities are generally directed to obtain symptomatic relief. The results are generally slow and uncertain. Due to the appearance of *tuberculosis cutis* on exposed areas with exacerbations during cold weather, and based upon the work of Duncan and Mariette on artificial fever in pulmonary tuberculosis, it occurred to us to apply local heat and general hyperpyrexia for these lesions. It was realized that inhibition of the growth of tubercle bacilli did not mean their destruction. The death-point temperature of these organisms is so high that local necrosis would occur if the skin were treated to this level with local heat. General hyperpyrexia at death point temperature of the bacilli is incompatible with life of the host.

The method of treatment consisted of general hyperpyrexia in one case and local heat with infrared lamp in all cases. When local treatment was used, the temperature of the skin was the maximum that could be tolerated by the patient. Occasionally vesiculation occurred. The duration of treatment varied from one-half hour to four hours or more per day.

A variety of types of tuberculosis of the skin were treated by these methods. Biopsies were taken before treatment and guinea pigs were inoculated with ground tissue or pus in all cases. Tissue inoculations were made on culture media, and ground tissue was injected into cold-

[1] Presented at the Mississippi Valley Conference on Tuberculosis, Madison, Wisconsin, September 12–14, 1935.

blooded animals in some cases. This was done in an attempt to determine if a type of organism, which caused lesions to appear on exposed parts of the body, especially during cold weather, would grow at lower than human body temperature. Cases 1 and 2 were biopsied, injected intraperitoneally and into the dorsal lymph-sac of frogs and also intraperitoneally into guinea pigs. Controls were used. Autopsies of these animals in six weeks were negative for tuberculosis. Ground biopsies of these same lesions were inoculated on Herrold's glycerine-egg medium after the specimens had been treated by the method recommended by Sweany, that is, specimens were treated with 3 per cent hydrochloric acid and neutralized with sodium hydroxide. These cultures so treated were kept at room temperature and at 98°F., and resulted in no growth in eight weeks. Temperatures were taken with thermocouples at 25 exposed areas of the skin of three patients reported and a group of controls. The results of these readings indicated that there was little if any difference between skin temperatures of the controls and these cases, in spite of the erythrocyanotic appearance and clammy feel.

The following is a summary of cases treated by heat:

1: Multiple benign sarcoids of the skin. A. A., white, male, aged 31, admitted to Glen Lake Sanatorium in 1930 with far-advanced pulmonary tuberculosis and tuberculosis of the right sacroiliac joint of six years' duration. Cutaneous eruptions, present and progressive over 5½ years, consisted of discrete papules of split-pea to bean size, and plaques involving the skin of the face, scalp, neck, upper extremities, chest and left thigh. The color of the papular eruption in the majority of the lesions was not unlike that of the surrounding skin. There was, however, a definite yellow-brown discoloration, and a few lesions were capped by thin adherent scales. The plaque-like lesions, round and oval, slightly elevated, varied in size from a dime to a quarter and were made up of closely studded papules similar to the previous description. Some of these lesions with a central atrophic scar were studded at the periphery by split-pea-sized papules. The color and surface change were similar to those of the individual papular lesions. Previous treatment consisted of bed-rest, ointments, lamp, sun, superficial X-ray therapy and neoarsphenamine, all of which had produced little change in morphology of the lesions.

The tuberculin test, Dorset's O. T., 0.001 mgm., was positive once, and negative on repetition. Sputum examination was positive for tubercle bacilli. The Kolmer and Kline tests were negative. Four guinea pigs were injected with two biopsy specimens with negative results in six weeks. These biopsies had characteristic findings of a multiple benign lupoid.

Treatment: Local treatment was instituted on March 21, 1934, and con-

tinued for 9½ months. Each lesion was treated with an infrared lamp for about half an hour a day, the distance being determined by the point of tolerance.

Progress: The patient was discharged on November 30, 1934. At that time the lesions of the arms, chest, neck and thigh had undergone involution. The lesions of the face were nearly healed. The site of the involuted lesions remained as a slightly depressed atrophic scar with a surrounding zone of *erythema ab igne.*

2: Erythema induratum and papulonecrotic tuberculosis of the skin. S. M., white, female, aged 16, readmitted to Glen Lake Sanatorium, May 9, 1934, with a history of calcified childhood tuberculosis of several years' duration. Six years previously, the patient developed lesions over the calves of both legs and three years ago pustular lesions on the hands and feet, most marked on the palmar and plantar surfaces. These eruptions increased in number during the winter months. The lesions of the legs consisted of various sized painless, oval or round subcutaneous nodules, 10 to 12 in number, varying in size from 1 to 5 cm., and in various stages of evolution and involution. The covering epidermis was vividly red, one lesion having a small central necrotic area exuding a seropurulent discharge. Interspersed between active lesions were many depigmented atrophic depressed scars surrounded by varying degrees of erythema and cyanosis. The pustular lesions of the hands and feet consisted of split-pea-sized, indurated, papular pustules in all stages of development, and cyanotic in color, the mature lesions painful and having a yellow necrotic centre. The healed lesions left pitted scars and on one finger the grouping of these scars caused a slight deformity. The upper and lower extremities were cold, clammy, and acrocyanosis was present. The patient had been given symptomatic treatment for 2½ years on her first admission to the Sanatorium for erythema induratum with some involution of the lesions; however, these reappeared upon discharge. In addition to this, the patient has received intravenous medications of neoarsphenamine, ointments, and supporting and protective treatment of the legs with very little benefit.

The tuberculin test, Dorset's O. T., 0.001 mgm., was positive. The Wassermann and Kline tests were negative. Biopsy of both types of lesions was performed on four guinea pigs and resulted in negative findings for tuberculosis at the end of six weeks. Microscopic findings of these sections from lesions of the legs were characteristic of erythema induratum and the lesions of the fingers of papulonecrotic tuberculosis of the skin.

Treatment was instituted on May 9, 1934, and consisted of local heat for four hours a day for one month, Sitz baths, and four general diathermy treatments. The latter were begun May 28, 1934, and rectal temperatures of 104°F. were obtained.

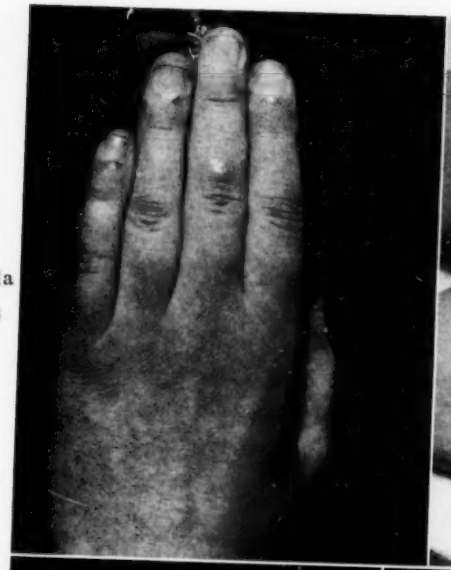

Fig. 1a

Fig. 1b

Fig. 2a

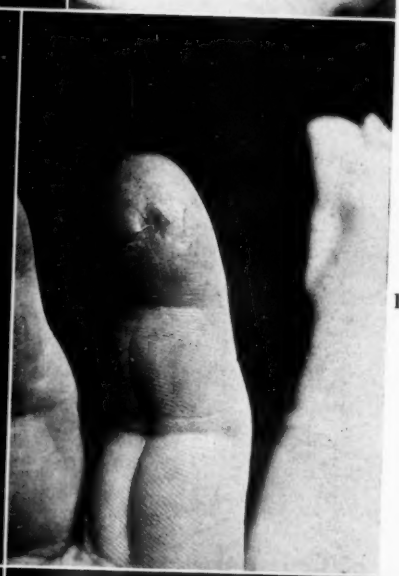

Fig. 2b

Fig. 3a

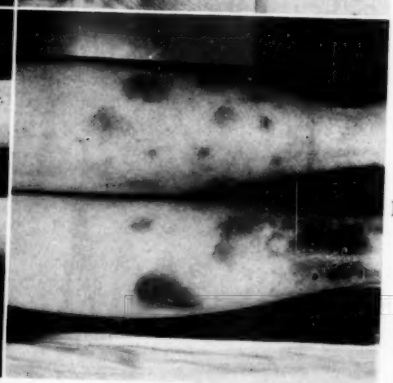

Fig. 3b

PLATE 1

Progress: The lesions of the hands and feet healed in less than three weeks. There remained only depressed hyperaemic scars. The eruptions on the legs were markedly improved and could be classified as quiescent, because the induration was more localized and had a consistency and size similar to those of the inactive lesions. There was, however, present, a definite erythema, the amount of which was difficult to determine because of the *erythema ab igne.* The patient has been under observation for a period of fifteen months and has had a few new lesions which responded in a few days to local heat as previously given.

3: Inoculation tuberculosis of finger. G. K., white, female, aged 59, was first seen by us on August 8, 1934, with a puncture wound of the palmar surface, terminal phalanx, right index finger, present for twelve weeks. She gave a history of injury and subsequent treatment by surgical incision and local medication. The lesion at the time of examination appeared as a painful punched-out ulceration on the terminal phalanx of the right index finger, 4 mm. in diameter and 5 mm. deep, surrounded by a brawny erythema and

PLATE 1

Fig. 1a. Case 2. March 24, 1934. Papulonecrotic tuberculosis of the skin (before treatment). There was no important change on May 9, 1934, the beginning of treatment.

Fig. 1b. Case 2. June 27, 1934. After treatment.

Fig. 2a. Case 3. August 15, 1934. Puncture wound infected with tuberculosis. Before treatment.

Fig. 2b. Case 3. January 25, 1935. After treatment. Wound closed now for three months.

Fig. 3a. Case 5. January 5, 1935. Erythema induratum. Before treatment.

Fig. 3b. Case 5. January 21, 1935. After treatment. Remains areas of hyperpigmentation.

oedema. The discharge from the wound was scanty and serosanguineous. There was no evidence of any other tuberculosis.

The tuberculin test, Dorset's O. T., 0.001 mgm., was positive before injury. The Wassermann was negative. A guinea pig inoculated with pus from the lesion was positive for tuberculosis at six weeks. Biopsy was not taken.

Treatment: Treatment consisted of dry heat by infrared lamp, one-half hour twice a day, and wet heat one-half hour a day.

Progress: The wound was healed with a good scar in two months with persistence of some pain for more than four months. The lesion now presents as a painless depressed puckered scar, with no evidence of activity.

4: Papulonecrotic tuberculides of fingers, etc. E. F., white, male, aged 28, was admitted to Glen Lake Sanatorium on July 10, 1934, with far-advanced pulmonary tuberculosis of three years' duration, and tuberculous enteritis. In September, 1934, patient had three attacks of a papulopustular eruption involving the terminal phalanx of the left index finger, the sole of the left foot,

and the 4th and 5th toes. During one of these attacks, he developed tender oedematous areas over the right forearm and leg. These were incised and found to be a tuberculous inflammatory process involving the intermuscular septa. The cutaneous lesions consisted of tender papulopustules, of split-pea size, and surrounded by a bright red inflammatory halo. The central portion of these contained pus. The previous treatment consisted of medicated packs.

The tuberculin test, Dorset's O. T., 0.001 mgm., was positive. The Kolmer and Kline tests were negative. Guinea-pig inoculation with pus from the lesion of the toe was positive for tuberculosis. The microscopic section of the lesion could be classified as an example of a papulonecrotic tuberculosis of the skin.

Treatment: Treatment with local heat was instituted for one month, with partial resolution of the cutaneous lesions. Because of surgery, treatment was discontinued for a time, and lesions reappeared. However, since that time treatment has been carried out daily and the eruption has undergone involution in some areas and improved in others.

5: Erythema induratum. P. S., white, female, aged 34, was admitted to Glen Lake Sanatorium on January 4, 1935. She gave a history of nodules appearing on the calves of the legs during the past eight years. Lesions consisted of various-sized subcutaneous painless nodules, 15 to 20 in number, and from 1 to 6 cm. in size, in various stages of development. The majority of these were oval and covered by epidermis which was a livid red. There were numerous areas which represented healed lesions in which there were depressed atrophic, depigmented and hyperpigmented scars. The remainder of the examination was normal except for a thickened pleura at the left base. The previous treatment consisted of internal, local and intravenous medications, without benefit.

The tuberculin test, Dorset's O. T., 0.001 mgm., was positive. The Wassermann and Kline tests were negative. Guinea-pig inoculations from the lesion on the left leg were negative for tuberculosis. Microscopic section of biopsy of a well-developed lesion was typical for erythema induratum.

Treatment: Local lamp treatment was instituted on admission for six hours a day for 18 days, and the patient was discharged.

Progress: All lesions at the time of discharge had undergone involution. There remained only firm, subcutaneous nodules. Erythema and cyanosis were absent. The residual eruption appeared as brown, hyperpigmented, depressed areas, conforming in configuration to the previous lesions. Three months later, several new lesions appeared and responded well after two weeks of treatment with heat, as previously described.

6: Lupus vulgaris. D. P., white, female, aged 18, born in England, was admitted to Glen Lake Sanatorium, January 18, 1935, with a tuberculous

spondylitis and tuberculous right sacroiliac joint of about 4 years' duration. The eruptions on the face, neck, ear, upper extremity, back and buttocks had been present for seven years. They were composed of discrete match-head-sized apple-jelly-like nodules arranged to form plaques, the largest of which involved the nose and central portion of the face, extending on to the septum and over the vermilion border of the upper lip. Similar types of lesions were found on other parts of the body, some with cicatricial scarring and a few active nodules in the scars. There was also a 1.5 cm. papilloma extending from the tip of the nose. Previous treatment with X-ray, pyrogallic acid, Gehrson-Sauerbruck diet, had given only fair relief.

The tuberculin test, Dorset's O. T., 0.0001 mgm., was positive. The blood serology was negative for syphilis. Guinea-pig inoculation with a portion of a nodule was negative for tuberculosis. Microscopic section was characteristic of lupus vulgaris.

Treatment: The infrared lamp is being used on the lesions of the face and right arm at the present. The response to treatment has been slow, but definitely one of improvement.

COMMENT

The results of this small series of cases indicate that some types (cases 2, 3, 5, 6) of skin tuberculosis may be benefited by treatment with heat. This, of course, does not mean cure. In case 1 the slower response of the lesions to treatment may well be due to the very short duration of the daily treatments. Case 4 represents a patient with a poor general resistance to a far-advanced systemic disease. The chronic or proliferative types show improvement which does not offer a great deal of encouragement over previous reported methods. The acute type, mainly papulonecrotic tuberculosis, erythema induratum, and inoculation types, respond well to this mode of therapy. The results may be due to the inhibition of tubercle-bacillus growth in the primary focus when generalized hyperpyrexia is used. This inhibition may be reflected in fewer lesions or absence of lesions for a period of time (case 2). The local heat, which was used in all cases, causes hyperaemia, phagocytosis and absorption. Inhibition of the microörganism must be considered. However, the resistance of the host is probably the most important factor.

In conclusion, we believe that the series is small and the observation time short to arrive at a definite conclusion, but the response in the reported cases was such that this type of therapy may well prove a valuable adjunct in the treatment of tuberculosis of the skin.

SIMULTANEOUS BILATERAL SPONTANEOUS PNEUMOTHORAX COMPLICATING PNEUMONOCONIOSIS

A Report of a Case, with a Review of the Literature[1,2,3]

L. GRANT GLICKMAN AND BENJAMIN H. SCHLOMOVITZ

The scientific study of pneumonoconiosis in the past ten years has been extensive, particularly by British, American and German clinicians (38) (51), roentgenologists (53) (55) (56) (57), pathologists (3) (21) (22) (23) (62), and experimentalists (28) (29) (47). This is especially true for the type known as *silicosis*, a progressive, fibrosing process in the pulmonary tissue and its lymphatic apparatus. Tuberculosis frequently complicates pneumonoconiosis. A second complication is vicarious emphysema. Another complication frequently observed, especially in the later stages of silicosis, is hypertrophy of the right heart. However, one complication which is not commonly mentioned in the literature on silicosis is that of spontaneous pneumothorax. Still rarer is simultaneous bilateral spontaneous pneumothorax on a pneumonoconiotic background. In a review of the literature very few authenticated cases of simultaneous bilateral spontaneous pneumothorax have been reported to date. To the references cited in McMahon's 1932 review (48) and to that of Oechsli and Miles (52), we have added a number that have been apparently overlooked, and wish to present another case thoroughly confirmed by clinical, roentgenological and pathological findings.

Case Report

A male negro, aged 40, coal-miner including rock-drilling in seven-month to ten-year periods from the age of sixteen to thirty-five, was hospitalized January 3, 1933, with the following complaints: productive cough, night-sweats, loss of weight, malaise, and dyspnoea as a chief disturbing factor, since 1929.

Past Medical History: Gonorrhoea and chancroid in 1919; pleurisy (left),

[1] From the Tuberculosis, Radiological and Pathological Services of the Veterans Administration Facility, Milwaukee, Wisconsin.

[2] Published in part in the *Medical Bulletin*, Veterans Administration, October, 1934, xi, no. 2.

[3] Published by authority of the Medical Director, Veterans Administration, Washington, D. C., who assumes no responsibility for opinions expressed by the authors.

1921; pneumonia, 1925; recurrences of the pleurisy from time to time following 1921, but no history of haemoptysis. Average weight for the past three years, 158 lbs.

Physical Examination on Entrance: Disclosed a well-developed, well-nourished man, not acutely ill; height, 68½ inches; stripped weight, 153 lbs.; pulse, 80; blood-pressure, 136/88; respiratory rates, 18 to 25; and the following abnormalities: accentuation of the second pulmonic sound; chest expansion, 2½ inches; supraclavicular fossae depressed; mobility of left side retarded; tactile fremitus increased bilaterally; breath-sounds on the right side, harsh throughout, with a few medium moist post-tussic râles on a level with the 3rd dorsal vertebra; on the left side, increased voice-sounds between the levels of the 3rd and 8th dorsal vertebrae, with harsh breath-sounds and broncho-vesicular breathing, scattered fine moist râles in the lower two-thirds, and pleuritic friction sounds in the base.

Laboratory Findings: Negative urine; negative blood Wassermann and Kahn tests; ten 24-hour sputum examinations for tubercle bacilli (8 by the antiformin method) were negative; haemoglobin, 98 per cent (Newcomer); red cells 4,960,000, and leucocytes 8,800.

Stereoscopic X-ray Films (January 3, 1933, figure 1): Revealed a broad thoracic cage with transverse intercostal diameter of 30 cm. Cardiac shadow prominent in region of left pulmonary artery, and the cardiac measurements (*MR* 4 cm.; *ML* 9 cm.) give a cardiac index of 43.3 per cent (not enlarged). Trachea in midline; hilum broad, with calcified nodule, 1.5 x 1.0 cm., in upper right perihilar area. Right stem-bronchus quite prominent. Costophrenic angle and right apex clear. Throughout the remainder of both lung fields there were small round densities varying in size up to 5 mm., with tendency to conglomeration in the middle third of the lung. The domes of the diaphragm were smooth.

Clinical Diagnosis: Pneumonoconiosis, second stage, and chronic pulmonary tuberculosis, far advanced, active, with chronic fibrous pleurisy of the left base. On this basis, the following pulmonary pathological condition was postulated: fibrocaseation, diffuse, left lung and right upper lobe, with fibrosis, and pleurisy of left base.

Clinical Course: At the end of the third month (March) there was a slight increase in the abnormal physical findings of the chest, and the weight had gone up to 169 lbs.

In the fifth month (May) the only noticeable change was a further increase in weight to 171½ lbs. X-ray examination (May 10, 1933) revealed no change in the cardiac shadow or position of the trachea. The nodulations in the middle third and in the peripheral zone were more confluent.

In the seventh month (July) pleuritic signs were detected in the right base.

In the ninth month (September) there was an increase in moisture in the right

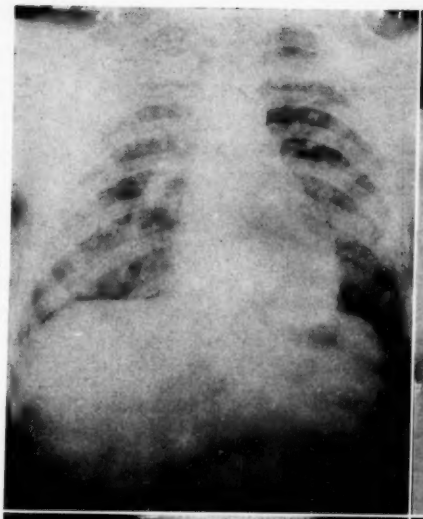

Fig. 1

Fig. 2

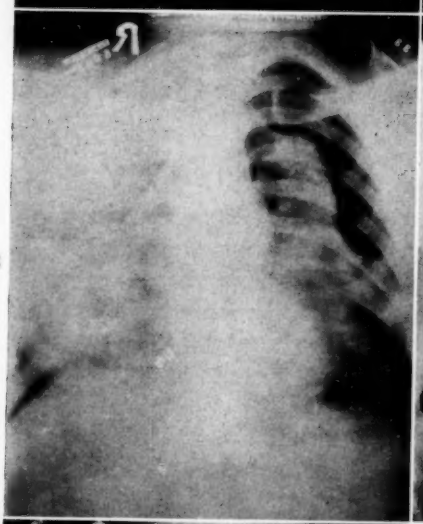

Fig. 3

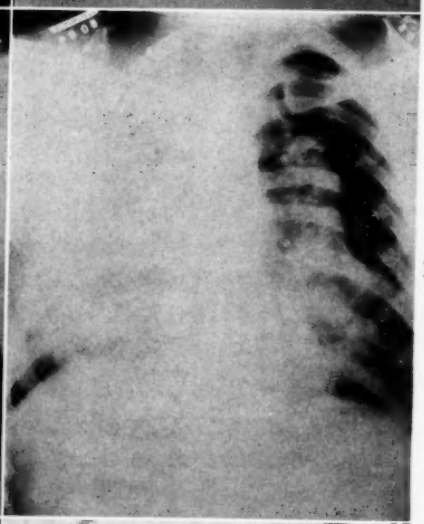

Fig. 4

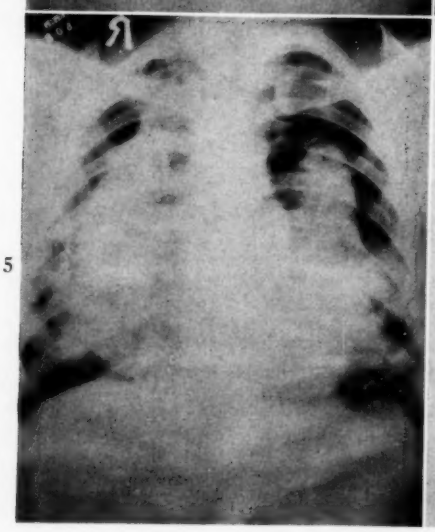

Fig. 5

Fig. 6

PLATE 1

lung; the pulse-rate was more definitely elevated, ranging from 80 to 108, with dyspnoea accentuated, and a definite beginning of loss of weight (167½ lbs.). It was then surmised that there was cavitation in the upper lobes bilaterally. X-ray films on September 7, 1933 (figure 2) showed that the only essential change was tenting of the right dome of the diaphragm (adhesions).

On October 17, following a quarrel with another patient, there was a distinct turn for the worse in the patient's condition, as manifested more particularly by prolonged respiratory distress (rate 25 to 40 per minute), followed several days afterward by an elevated pulse. Stereoscopic films taken two days later (figure 3) revealed retraction of the lower portion of the trachea to the right; a comma-shaped pneumothorax on the *left*, involving the apex and the peripheral zone of the 1st to 3d interspaces (anteriorly); a second left-sided pneumothorax in the peripheral zone of the 4th and 5th interspaces, with an adhesive band at the periphery of the 3rd interspace. The other findings in the left lung field were unchanged. Further coalescence of the nodulations were now evident throughout the right lung field.

PLATE 1

Fig. 1. January 3, 1933. On admission, second-stage pneumonoconiosis.

Fig. 2. September 7, 1933. Increase in pulmonary fibrosis; diaphragmatic adhesions.

Fig. 3. October 19, 1933. Left-sided spontaneous pneumothorax two days after onset.

Fig. 4. October 24, 1933. Right lung field shows increased density one week after the left-sided pneumothorax.

Fig. 5. December 21, 1933. Definite simultaneous right-sided pneumothorax two months later.

Fig. 6. January 29, 1934. Postmortem (A-P position), left pneumothorax more pronounced, with hilar structures and heart forced into right hemithorax.

One week later, October 24, 1933, X-ray examination (figure 4) revealed the left pneumothorax to be more extensive, with separation of the visceral and parietal pleura in the inner zone of the 1st interspace. By lateral examination, the pneumothorax was now visualized as complete except in the costophrenic-angle area, thus showing removal of the adhesive band noted previously. On the right, the lung field had become more radioöpaque except in the apex and costophrenic angle.

Physical examination now showed the breath-sounds distant to absent, amorphic in character, and an absence of moisture. At this time the sedimentation rate was 11 mm. at the end of one hour; haemoglobin, 112 per cent (Newcomer); red cells, 5,100,000; leucocytes, 15,400; and differential count, 56 per cent polymorphonuclears, 43 per cent small and large mononuclears, 1 per cent transitionals. Eighteen additional antiformin sputum examinations were still negative for tubercle bacilli. Of two guinea pigs inoculated, one was positive for tuberculosis. Repeated 24-hour specimens of sputa measured 5½ to 10 ounces.

Early in November, digitalis was administered for beginning congestive heart failure. At this time the *BMR* was +17 per cent; alkali reserve, 53 per cent; and body-weight, 160 lbs.

In the twelfth month (December) there was a marked exacerbation in coughing, followed in a few days by the evolution of cyanosis, increased dyspnoea, and right lower chest pains, with harsh amphoric breath-sounds throughout the right lung. There was still no marked change in body temperature. Stereoscopic X-ray films on December 21, 1933 (figure 5), disclosed no appreciable change in the position of the cardiac shadow. The trachea was now in normal position. On the left side the lung was still collapsed, with a decrease in the transverse diameter of the pneumothorax as it involved the 2nd and 3rd interspaces (anteriorly). Some expansion of the lower lobe was apparent, and the pneumothorax was noted as involving the extreme base anteriorly and posteriorly. There were adhesions in the left cardiophrenic angle. But, on the right side there was also a pneumothorax extending from the apex caudad to the 5th interspace, and involving the entire periphery between these areas. The right lung field was more radioöpaque. The right dome of the diaphragm was now smooth in outline, and without the tenting reported above.

The physical condition of the patient became progressively worse, and orthopnoea persisted after the development of the contralateral pneumothorax. Curiously, he got considerable relief by inhaling aromatic spirits of ammonia, besides being given morphine or codeine. At the end of the thirteenth month (January, 1934), which was six weeks after the spontaneous appearance of the second (right-sided) pneumothorax, marked abdominal distention and increased oedema of the extremities developed, with *exitus* on January 29, 1934.

Postmortem X-Ray Examination (figure 6): Revealed an extension of the left pneumothorax, with the cardiac shadow pushed over into the right hemithorax, leaving only the apex of the heart in the left hemithorax. The right pneumothorax had become partially absorbed, being present only at the diaphragm. The lung markings on the right were indistinct.

Postmortem Findings

Individual, well nourished; dependent oedema, especially in the lower extremities, and subcutaneous oedema.

Chest: Barrel-shaped; perioesophageal lymph nodes enlarged and black; inferior mediastinal lymph nodes prominent; peritracheal lymph nodes enlarged and cut with resistance; tracheobronchial and bronchopulmonary lymph nodes, enlarged tremendously, dark grayish-black, and cut with considerable resistance. The lymph nodes on the left were relatively less involved.

Lungs: The bronchiolar and peribronchiolar lymph nodes were enlarged, firm, and black and gray; the left lung was collapsed and fairly solid throughout

(except for the lower left portion of the upper lobe and free edges, including the apex which showed bullous emphysema). The left apex was held up by a long narrow strand of fibrotic tissue which was attached to the sheath of the left subclavian artery. Both pleural cavities were relatively free from fluid. The roughened visceral pleura was markedly thickened throughout. The right lung, particularly the upper lobe, was markedly adherent to the parietal pleura posteriorly; the right lower lobe was adherent to the diaphragm; the right upper lobe was blackish-gray (slate-like), except for the free portions, which were dark purplish and red, while at the free edges there were numerous raised and distended light pink areas; the right upper and middle lobes were noncrepitant and firm, while the right lower was crepitant. *On Section:* The right lower lobe was blackish-pink, and cut with increased resistance, exuding a moderate amount of frothy fluid; the right upper lobe cut like firm sclerotic tissue, gritty to the knife edge, indicating either calcification or considerable pneumonoconiotic infiltration of the tissue; there was generalized obliteration of the normal alveolar spaces, with no bronchiectatic cavities; in the right lower lobe there were a small area of calcification, and, surrounding one of the larger adjacent bronchioles, a larger area of calcific deposit. The left lung was slate-gray and dark-red, with a restricted area (4 x 3 x 2 cm.) of greenish-gray discoloration (caseation) close to the root of the lower lobe.

In addition to the collapsed left lung, with adhesions and vicarious emphysema, gross examination showed generalized pulmonary fibrosis, right-sided compensatory pulmonary emphysema, slight hypertrophy of the spleen, enlarged liver with chronic passive congestion and cirrhosis, chronic myocarditis, and hypertrophy of the right ventricle.

Microscopic Findings: Lymph node: Foreign pigmentary deposits; node disorganized; several pink-staining, homogeneous areas with typical giant cells; fibrosis of tuberculous and pneumonoconiotic lymph nodes. *Lungs: 1:* Collections of foreign, brown, pigmented material packed in large mononuclears and fibroblasts as well as in free spaces; in massive areas phagocytic cells loosely disposed or packed in large areas and shadows of air-sacs, whose walls were thickened by large cells; many air-sacs filled with debris, cells, and homogeneous eosin-staining material (necrotic tissue and hyaline material); large collections of small round cells; and layered fibroblastic tissue forming nodules: —Pneumonoconiotic lung. *2:* Pleura markedly thickened; vessels prominent and engorged, some surrounded by fibroblasts, mononuclears and lymphocytes; subpleural air-sacs markedly dilated; black pigmented spots; air-sac walls thickened mainly by fibroblasts; many air-sac walls finer in texture than in the deeper areas.—Generalized extensive fibrosis (fibrotic pleura) and emphysema. Sections stained also with the Van Gieson connective-tissue stain and for tubercle bacilli confirmed these observations.

By a method of incineration of histological sections and the use of polarized light, collections of silica crystals were found predominantly in the areas of nodular fibrosis.

An analysis of the clinical record disclosed that death occurred because of cardiac failure (chronic myocarditis with right-sided hypertrophy) produced by pneumonoconiosis (chronic silicosis), advanced, third stage, with anthracosis; and complicated by a beginning tuberculous infection.

In this case the pathological findings presented two significant alterations at the surface of the lungs, either sufficient for the production of spontaneous pneumothorax. These were a sharply restricted minimal tuberculous necrosis and an extensive bullous emphysema, the latter secondary to a tremendous, generalized, dense, pulmonary fibrosis on a pneumonoconiotic basis. Owing to the fact that the patient survived the second contralateral pneumothorax for a period of six weeks, it would be purely speculative to say which of these was the cause.

DISCUSSION

Pneumonoconiosis: The recent bibliography on pneumonoconiosis (12) has been quite complete, and roentgenological (53) (55) (56) (57) and pathological investigations (3) (21) (22) (23) (62) have been quite extensive. Roentgenologically, the disease has been divided, according to the American classification, into three stages (except for the type produced by granite which has been divided into only two stages, an early and late stage). The *first stage* is characterized, roentgenographically, by an increase in the prominence and extent of the hilum shadows, an increased prominence and thickening of the trunk-shadows and a greater prominence of the linear markings of the peripheral zone. The *second stage* is represented roentgenographically by distribution of small, rounded densities, varying in size from pin-head to pea, distributed throughout both lung fields. These nodules often appear on the right side, usually about the hilum, and then later are perceptible on the left side. They are always more numerous about the hilum. There is always more or less evidence of a diffuse fibrosis or accentuated arborization. The *third stage* has been characterized by a predominance of diffuse fibrosis due to the coalescence of the nodulations. The nodulations are often larger than in the previous stage and have the appearance of irregular masses. They may be found close together, with a haziness intervening between

the individual masses. These may resemble the shadows as seen in tuberculosis or the changes may have the appearance of large tumor masses. At the same time, pleural changes are evident, associated with diaphragmatic involvement. Localized areas of emphysema may be present. Enlargement of the right heart occurs and the cardiac shadow may be displaced or distorted by the fibrotic changes.

Pneumothorax: The latest résumé of the causes of *unilateral* spontaneous pneumothorax can be found in a paper by Leggett, Myers and Levine (40). This type has been described extensively from the period of Itard in 1803 (33), and Laennec in 1819 (36), to that of Emerson in 1903 (16), and Hirschboeck in 1931 (31).

Spontaneous pneumothorax, in contrast to artificial pneumothorax, denotes the introduction of air into the pleural cavity through a pulmonary fistula. The pulmonary fistula which creates the pneumothorax is usually of small calibre, the result of which is that it very often becomes closed in the retraction of expiration but opens again in the succeeding inspiration, giving rise to the valvular or closed type of pneumothorax. If the fistula does not close in expiration the pneumothorax is called the *open type of pneumothorax.* This type is due to a fistula of a slightly larger calibre than of the previous type and is probably caused by the breaking down of a relatively larger lesion.

Bilateral spontaneous pneumothorax has been subdivided into the successive and simultaneous types. According to Olbrechts (54), the successive type of bilateral spontaneous pneumothorax indicates one in which a spontaneous pneumothorax occurs first on one side and then, later, the occurrence of a second spontaneous pneumothorax on the other side. The simultaneous type, in contrast to the successive type, is one in which the second pneumothorax occurs very soon after the first one and while the latter is still unabsorbed. In the majority of cases the aetiology is obscure, regardless of type. After ruling out the traumatic in origin, spontaneous bilateral pneumothorax occurs, in order of frequency, as due to the following conditions: Tuberculosis (4) (7) (14) (24) (25) (27) (45), emphysema (26) (46) (59) (63), pneumonoconiosis (1) (10) (13) (50) (51) (60), bronchopneumonia (15), asthma (17), congenital cysts (35) (44) (52), tumors (19) (20) (49), and interstitial fibrosis (8). A few cases have been checked repeatedly for many years by reliable clinicians and radiologists, and have apparently been definitely nontuberculous, although other lung pathological pulmonary conditions could not be

strictly ruled out because the cases survived. These are of the type known as *idiopathic* (2) (9) (30) (41) (42) (43) (44) (48). They truly come second in order, following tuberculosis as an aetiological factor.

Practically all cases of bilateral spontaneous pneumothorax with advanced pulmonary disease and tuberculosis are immediately fatal. Our case survived six weeks, and the clinical findings were verified by repeated roentgen studies and finally by postmortem examination. In addition, this case of advanced chronic silicosis was closely observed when the first definite indication of a tuberculous complication was detected, and when the acute cardiac breakdown occurred about three weeks after the first spontaneous pneumothorax. It is to be noted that practically every clinical observer on this case made a diagnosis of far-advanced pulmonary tuberculosis. The autopsy, on the contrary, disclosed a sharply localized minimal tuberculous lesion, with the pneumonoconiotic fibrosis as the dominant pathological process.

The cases of Faschingbauer (18), Hayashi (26), Massini and Schonberg (46), Recamier (59), and Schmincke (62) were cases complicated by emphysema, and ended fatally.

The case of Emerson (17) was due to asthma, which also ended fatally.

The cases of Kjaergaard (35), Markson and Johnson (44), and Oechsli and Miles (52) were due to congenital cysts.

The cases of Borchard (6), Briggs (9), Fleischmann (20) and Radek (58) were those associated with malignant tumors and their metastases.

Bowen (8) reported a case of obscure aetiology upon a fibrotic pulmonary background, with resulting bilateral spontaneous pneumothorax.

The first case of simultaneous bilateral spontaneous pneumothorax complicating pneumonoconiosis was reported in 1929 by Chiale (10). This was of a miner, who had fifteen years' experience in various iron-ore mines in this country, after which time he became ill and returned to his native country, Italy. One year after his return to Italy roentgenograms disclosed bilateral spontaneous pneumothorax. Later this case became complicated by tuberculosis. A second case was reported in the same year by Reichmann (60)

In 1930, a third case was reported by DeLombardy and Pasquet (13), in a miner who had worked in both gold and quartz mines for a number of years, with varying intervals of granite mining. A roentgenogram revealed bilateral spontaneous pneumothorax upon a third-stage pneumonoconiotic background.

Norris and Landis (51) in their *Diseases of the Chest* reported a fourth case of a miner in the hard-coal industry, with a history of exposure over a period of twenty years. Upon admission to a sanatorium (11) he was in a terminal condition, and roentgenograms revealed bilateral spontaneous pneumothorax upon a third-stage pneumonoconiotic background. Frequent aspirations of air on both sides failed to reëxpand the lungs. Repeated sputum examinations were negative for tubercle bacilli. The case ended fatally.

In 1933, Abraham (1) reported a fifth case, that of a left-sided pneumothorax in pneumonoconiosis. After a lapse of nine months the case became one of bilateral spontaneous pneumothorax.

In 1934, Möller (50) reported a sixth case in a man, aged 62, who had worked in the porcelain industry for forty-seven years. Presenting himself in routine examination, the roentgenograms showed bilateral spontaneous pneumothorax upon a third-stage, silicotic background. This case ended fatally.

Ickert (32), considering the aetiology of spontaneous pneumothorax in pneumonoconiosis, stated that he and Redeker found that spontaneous pneumothorax in pneumonoconiosis is found only when the pneumonoconiosis is associated with tuberculosis. Abraham (1), quoting Bohme and Lancanus, states that the latter had observed four cases which ended fatally from pneumothorax in tuberculosilicosis.

SUMMARY

1. We have reviewed a rare case of extensive bilateral simultaneous spontaneous pneumothorax, thoroughly authenticated by clinical, roentgenological and pathological examinations. This case lived six weeks after the second contralateral pneumothorax.

2. The basic pathological process was a dense, generalized pulmonary pneumonoconiotic fibrosis with a quite recent restricted acinose tuberculosis.

3. The distinctive pneumothorax-inducing areas were a bullous emphysema or a tuberculous necrosis.

4. The bibliography of simultaneous bilateral spontaneous pneumothorax is *emended* to date. To the previously reported 77 cases by Oechsli and Miles, we have added from the literature another case to be listed under congenital cyst, and three more cases complicating pneumonoconiosis. Another case, presented herein, is also added under the

pneumonoconioses. This brings, to date, the total number of cases to 82, tabulated as follows:

Simultaneous bilateral spontaneous pneumothorax

AETIOLOGICAL FACTOR	NUMBER OF CASES	APPROXIMATE PERCENTAGE
Pulmonary tuberculosis	39	48
Idiopathic	17	21
Emphysema	10	12
Pneumonoconiosis	7	9
Congenital cyst	3	3
Bronchopneumonia	2	2.5
Malignant tumor	2	2.5
Bronchiectasis	1	1
Interstitial fibrosis	1	1
Total	82	100

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THE INDICATIONS FOR TERMINATING ARTIFICIAL PNEUMOTHORAX

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With our increasing knowledge of the value of pneumothorax in compression therapy, there has been a steady increase in the number of cases of tuberculosis receiving this form of treatment throughout the country. In 1920, when the Blue Ridge Sanatorium was opened for the reception of patients we gave pneumothorax to only 12 to 15 per cent of the cases admitted. During the last fiscal year, which ended June 30, 1935, an attempt was made to collapse the lungs by this method in 40 per cent of our adult patients. Other similar institutions have also shown a steady increase in the number of collapse cases; but there does not seem to have been during this time much thought given to the correlation of ideas as to how long cases should continue collapse, and what the guiding factors should be in reaching the decision to discontinue it. Also, it is found that a search of the literature gives very little help. Most of the articles written on artificial pneumothorax have generously advocated its use, giving glowing accounts of its therapeutic virtues, dealing somewhat with complications, but woefully neglecting to express an opinion as to the duration. Experience in pneumothorax work, however, enables one to realize the wisdom of this, for, after all, it is not unlike other features of tuberculosis work in that the individual case must be the criterion.

It would seem best to deal with this subject under two general headings. The first will refer to those cases in which pneumothorax had to be discontinued because of some complication, or because reëxpansion took place without the knowledge of the clinician. This we will call *Undesirable Reëxpansion of the Lung*. The second heading will deal with those cases of relatively long standing with a good therapeutic collapse that is well under control, and the patient apparently has an arrestment of the disease. This we will call *Voluntary Reëxpansion of the Lung*.

UNDESIRABLE REËXPANSION OF THE LUNG

Progressive obliteration of the pleural space will develop even under high intrapleural pressure of air. Too long an interval between refills,

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or too small a refill may allow the lung to come out and form contact with the chest-wall. When the pleural membranes have been artificially separated there is a strong tendency for them to adhere when they again come in contact, particularly so in some cases. It sometimes happens, for an unexplained reason, that the absorption of gas is unexpectedly rapid, and at a rate out of proportion to that previously experienced with that case. This is more apt to happen with patients who are coughing more than usual, or are taking more exercise. Once the lung touches the chest-wall, the pleural membranes become rapidly adherent and obliteration of the pneumothorax is the result. (See case report 4.)

In "selective collapse," expansion may easily take place in the same way, since the lower lobe is only partially collapsed and swings out and adheres to the lateral chest-wall, or to the diaphragm below. Also, collapse may be lost through obliterative pleural adhesions in chronic effusions. After fluid has been present for several months, it may become thick; heavy fibrin sediment which is present organizes, pleural adhesions are produced, and the lung is gradually drawn out to the chest-wall. Expansion of this type takes place from below upward, and usually begins in the costophrenic angle. After seeing a few cases of this type, one wonders whether it is not advisable to aspirate routinely the fluid, when it is sufficient in amount, and to replace it with the necessary amount of air.

When the fluid persists in reforming and becomes uncontrollable, Morrison Davies (1) advises discontinuing the artificial pneumothorax, aspirating the fluid, and substituting oleothorax to maintain the compression of the lung.

There are few cases of tuberculosis requiring pneumothorax treatment in which the disease is purely unilateral. The reactivation of an old lesion in the contralateral lung or the development of new disease is a constant source of annoyance, and is responsible for having to stop compression in many cases. When there is a small, or even a moderate-sized lesion, without much evidence of excavation, located in the contralateral lung above the 2nd rib, pneumothorax will usually prove successful. On the contrary, if there is much disease in the lung field opposite the root zone or in the lower lobe, continued compression is fraught with danger, especially if the collapse is maintained at more than from 50 to 60 per cent.

Rubin (2) reports end-results in 324 cases of pneumothorax of two to fifteen years' duration. All were far advanced except a few minimal and moderately advanced cases, in which collapse was used in treating

uncontrollable haemorrhage. In 102, or 31 per cent, of the cases, pneumothorax had to be discontinued in less than three months' time, due mostly to dense adhesions obliterating the pleural space. Rubin feels that, next to traction from heavy adhesions drawing the lung out and making further successful pneumothorax impracticable, effusions becoming empyematous and reactivation of disease in the opposite lung are about on a parity as a cause of reëxpansion.

Myers and Levine (3) have reported 52 cases of tuberculosis in children treated by pneumothorax. Some of the cases have been treated for several years, but at the time the report was made eleven of this number had been discontinued for the following reasons: seven on account of spread of the disease to the opposite side, three due to the formation of obliterating pleural adhesions, and the remaining patient was killed accidentally.

It often happens that the normal lower lobe of a lung can be completely compressed. Dense adhesions, either in the subscapular region or laterally in the region of the 3rd and 4th ribs, prevent collapse of the disease in the upper lobe where it is needed most. High intrathoracic pressure, in which there is definite danger of rupturing the lung, will occasionally cause the air to dissect around and through the adhesions, giving a partial collapse and fair therapeutic results to a small number of cases. (See report on case 1.) In past years we have persisted with this type of case sometimes indefinitely, hoping something could be accomplished. Almost invariably fluid will form which persists in spite of frequent aspirations. Eventually, tuberculous empyema develops, and the clinical course is unfavorably influenced. We now recommend the discontinuance of refills in these cases, and allow the lung to reëxpand, with perhaps advice regarding some other form of surgical collapse. A localized upper thoracoplasty is always to be preferred to a poor pneumothorax in this type of case.

Minnig (4) says, "The formation of pleural adhesions is the one insurmountable barrier to successful pneumothorax, and when this makes successful collapse impossible some other form of collapse should be tried."

Internal pneumonolysis is now being successfully used in certain types of pleural adhesions. When the pleural membranes are almost universally adherent by dense, resistant adhesions, this treatment is of no avail. It often happens that a cord, string-like, or even a broad-band type of adhesion may anchor the partially compressed lung to the chest-

wall overlying an open cavity. If the adhesion can be successfully separated by the electrocautery and a good collapse obtained, more drastic measures to accomplish satisfactory results may be avoided. (See case report 2.) Drash (5) has, by the separation of adhesions through the thoracoscope, enabled us to close cavities and proceed successfully with cases which otherwise would have reëxpanded and terminated unfavorably.

Our results in pneumonolysis, to date over a four-year period, are as follows: Total number of cases operated upon, 59; in 6 of this number the work was only exploratory, as the adhesions were of the type which could not be separated; of the remaining 53 cases, 28 had cavities, and 27 of this number were closed after the adhesions were cut. Twenty-five cases were without cavities, but adhesions were preventing the collapse of heavily infiltrated or consolidated areas. Of this number the adhesions were successfully cut in twenty-three. Thus, of the 53 cases in which division of adhesions was attempted, 50, or 94.5 per cent, were successfully separated. These results were based upon the following observations: Stereoscopic X-ray study of the lung after operation, change in the sputum from positive to negative, gain in weight, improvement in appetite and digestion, reduction in amount of air required, and lengthening of the interval of refills. From these results it would appear that before allowing a lung to reëxpand due to adhesions, one would be justified in having a thoracoscopic study made with the idea of having the adhesions separated if they are of a suitable type.

VOLUNTARY REËXPANSION OF THE LUNG

Under this heading we usually find cases of long-standing collapse. Complications, if they have existed, have been mastered. The compression has been considered successful in that all symptoms are gone, the sputum is negative for tubercle bacilli, and the lung, from all external appearances, is apparently healed.

When the physician can safely advise reëxpansion and still feel his results will be durable is the point at issue. Further, upon what fundamental factors must this decision rest? It is not the healthy areas of lung tissue that have been under collapse that will give trouble, for they will usually reëxpand, be unchanged and proceed to function as formerly. The old diseased areas, perhaps with a cavity which was present before collapse, will give considerable concern as to whether it will be found healed and free from future harm. Also, some anxiety may be felt

as to the possibility of the development of post-reëxpansion complications, and, if so, how they can best be handled.

It has been repeatedly stated that a successful pneumothorax in a minimal case should continue compression for from one to two years; in a moderately advanced case without much evidence of cavitation, for from two to three years; and in a far-advanced case with cavity-formation, five or more years. Many cases that are seriously ill before collapse make such a splendid recovery under this form of therapy that it seems unwise to both the physician and patient to ever permit reëxpansion of the lung.

Dufault and Laroche (6) have made a survey of 65 of their cases of clinically effective pneumothorax. Each one of their cases, starting with demonstrable cavities and positive sputum, had gained weight, and were afebrile and bacilli-free at the end of treatment. All but eleven were reëxpanded at the end of five years. Some of this number were voluntarily discontinued, but most of them were stopped due to progressive obliteration of the free pleural space. Eighteen, or 27 per cent, of the cases were collapsed one year or less, and within two to three years 66 per cent had relapsed. Nineteen, or 29.3 per cent, were collapsed one to two years, and 42 per cent relapsed within three years. Fifteen, or 23 per cent, were collapsed two to three years, and 53 per cent relapsed within three years. Thirteen, or 20 per cent, were collapsed over three years and only 15.4 per cent of them suffered relapse.

In 1932 deWeck (7) reported 51 cases treated by pneumothorax and observed over a period of two to nineteen years after reëxpansion. In this group, of those collapsed less than one year, 34 per cent relapsed; of those collapsed one to two years, no cases relapsed; of those collapsed two to three years, 16 per cent relapsed; of those collapsed three to four years, 14 per cent relapsed; of those collapsed four to seven years, 7 per cent relapsed; and of those collapsed eight to ten years, no cases relapsed. So it will be seen that the striking feature in both of these reports is the almost constant decrease in the percentage of breakdowns after reëxpansion, as the number of years which collapse was maintained is increased. Premature discontinuance of compression seems to be practised in too large a percentage of cases for patients to get the maximum benefit from this treatment.

Inconvenience and expense to the patient in obtaining refills may prove to be a major issue in deciding to terminate the treatment. In some sections of the country an experienced operator may not be available

when the patients return home from the sanatorium. The fatigue of travelling perhaps a hundred miles, once every week or ten days, for refills may be more harmful to the patient than the beneficial effects derived from the collapse. The cost of the refills must also be considered, and may be too heavy a burden to bear.

The condition of the lung before collapse is one of the most important points in considering reëxpansion. No case should be voluntarily terminated without first reviewing the old X-ray films, and making a close study of the physical signs and clinical course prior to compression. If extensive disease with a large area of excavation and marked toxic symptoms were present, then the decision becomes more difficult to make. Also, if compression was instituted to control haemorrhage there is always the fear on the part of the patient that the bleeding will recur when the refills are stopped.

The extent and kind of pathological process in the lung before collapse should be studied. An exudation—a fairly recent infiltration without cavitation—but which was proved to be progressive before collapse, is expected to regress and to resorb in a relatively short time. Conversely, the old fibrocaseous type with thick-walled cavities requires a long period of time to heal, and a minimum of five to six years of collapse is required after the sputum has become free from tubercle bacilli.

BLOOD STUDIES

Much can be found written on the qualitative changes in the blood of patients under pneumothorax treatment. Some of these changes appear to be of value and are worth mentioning; others are apparently valueless. The red-cell sedimentation rate is perhaps the most widely used test at present, and some clinicians seem to rely on it almost to the exclusion of the clinical course of the patient in determining the presence or absence of activity in the collapsed lung.

Harper and Jennings (8) have this to say, "The red cell sedimentation rate is an invaluable method of determining unhealed areas in a lung collapsed by artificial pneumothorax. We are so sure of its value here that we continue the compression treatments until the rate is normal regardless of any other evidence indicating a healed lesion."

In determining when a collapsed lung has healed and in a condition to reëxpand, Medlar (9) lays great emphasis on the "leucocytic reaction." He determines the relationship existing between the neutrophiles, lymphocytes and mononuclear leucocytes (monocytes). An increase

in neutrophiles to him means abscess-formation or excavation; an increase in lymphocytes signifies healing; and an increase in monocytes means an increase in tubercles and spread of disease. This at first seems difficult to interpret, but Medlar gives a graphic system to be used and a normal and abnormal ratio of the cells which makes for simplicity. He reports cases supporting the value of this system.

Dugan (10) uses this "leucocytic reaction" blood count of Medlar's, and reports 52 cases of far-advanced disease before collapse on which it was used before reëxpansion. Of the number which had a favorable blood picture, 44 per cent were found to be healed on reëxpansion, and 40 per cent of the remaining number which made fair progress under collapse therapy showed a slightly septic blood graph.

Neal (11) recently reported some work, advocating allergy as a guide in terminating pneumothorax. In making this study, a group of 30 cases was selected. These patients had been having pneumothorax treatments over a period of from eight months to eight years. All were proved cases of tuberculosis, as they had tubercle bacilli in the sputum and X-ray evidence of cavity formation prior to the beginning of compression therapy. The intracutaneous tuberculin test was used, beginning with 0.001 mgm., on the flexor surface of the forearm. Unless a positive reaction was obtained, Neal gradually increased the amount until a maximum of 10 mgm. was given. Twenty-two cases were gradually eliminated as their tests became positive, but eight were negative to the highest dosage used. In this group of negative reactors refills of air were discontinued and, when their lungs had almost reëxpanded, they were tested a second time, this time only 1 mgm. and 10 mgm. injections of tuberculin being used. One of the 8 cases that had been compressed only eleven months gave a positive reaction. The remaining seven continued negative to 10 mgm. of tuberculin six months after complete reëxpansion, and, in addition, the X-ray reports showed no pathological activity in the reëxpanded lung.

Neal feels that, regardless of the extent of the original lesion, and the period which collapse has been maintained, one is not justified in permitting reëxpansion until allergy to tuberculin is lost. He also believes that, by using the tuberculin test, we may be able to discontinue collapse therapy much sooner in from 25 to 30 per cent of cases under treatment, and to get them back to a status of an economic asset rather than have them continue on indefinitely as a liability.

The chief argument against this work is found in the well-known fact

that most adults will show a positive tuberculin test in the absence of any clinical or X-ray evidence of active tuberculosis. It is entirely possible that this test may be of value in those cases which show a negative tuberculin test after a prolonged pneumothorax treatment.

DANGER OF REËXPANSION FOLLOWING PNEUMOTHORAX

As simple as it may appear, no one can foretell before reëxpansion the true condition of the collapsed lung and what complications may arise from reinflation. The normal elastic tissue has, to a great extent, been destroyed by the disease and is replaced by fibrous tissue, the characteristic of which is that it is continually shrinking, thus producing localized areas of atelectasis. As a result, there is a diminution in volume of the lobe, with no change in the intrathoracic space where it is located. If no pleural adhesions are present, the contraction of the fibrous tissue in the adhesion cannot pull the lung out to the chest-wall; so, instead, the lung shrinks to the fixed point which is the hilum. Thus the diseased portion of the lung is prevented from reëxpanding by fibrosis, and is little affected by the increasingly negative intrathoracic pressure as the air is absorbed. Consequently, the portions affected are the more or less mobile trachea, heart and mediastinal structures which are drawn to the involved side. (See case report 5.)

If, prior to collapse, the lesion has been located in the upper lobe and was not too extensive, the traction force will be confined to the upper thorax and will displace only the trachea, large bronchi and root-zone structures. Lower-lobe lesions on reëxpansion following pneumothorax may cause torsion and displacement of the heart and great vessels in the mediastinum, but these changes are usually of no consequence. All those who have had experience in administering pneumothorax know that the heart is often displaced into the opposite thorax, sometimes markedly so, without causing discomfort to the patient. Hansen and King (12) have essentially substantiated this view with some work which they did on the influence of pulmonary collapse on the electrocardiogram. On the contrary, when the trachea and large bronchi are distorted and displaced, there is dyspnoea, a choking sensation; and often a mechanical asthma develops. If there has been much tuberculosis present, even though the disease has apparently become arrested from collapse, a residual catarrh from a secondary bronchitis causes the mucoid secretions to continue. If drainage of these secretions is interfered with by obstruction in the root zone, toxaemia will develop.

From this it will be seen that, when a decision has been made to allow a lung to reëxpand, there are many unfavorable and annoying conditions, which may develop, that will need immediate attention. Frequent fluoroscopic studies should be made during the period of reëxpansion, serial stereoscopic roentgenograms taken, and close clinical observations made. Perhaps the method of choice is to lengthen the interval between refills, and reduce the amount of air one-third to one-half at the time of each subsequent injection over a period of three or four months rather than to stop the refills summarily. In this way the reëxpansion of the lung will be gradual, and an opportunity will be given to study the diseased areas to see whether they are healed before the pleural space has become completely obliterated and thus make recollapse impossible if it is found necessary later. Also, the trachea and mediastinal structures may be observed closely, and, if some remedial measure is necessary to prevent disabling displacement, this may be done early.

We are inclined to believe that most cases that have been completely collapsed over a period of several years will have some permanent atelectasis, and, to prevent trouble from too much displacement, a phrenic interruption should be performed. This operation is easily and safely done in the hands of a capable and experienced surgeon. It would seem advisable to have the nerve crushed at first, and, if the results are satisfactory, the operation may be repeated, or perhaps the nerve evulsed, thus producing permanent paralysis of the leaf of the diaphragm on the affected side.

Davies (1) has this to say, "There is one procedure which can help considerably to lessen the risks attendant on abandoning an artificial pneumothorax. If the dome of the diaphragm is paralyzed, its rise will diminish the size of the thoracic cavity and reduce the subsequent strain on the expanding lung."

In a pneumothorax which has been long established, and in which a large single cavity or multiple cavities have existed prior to collapse, Davies (1) believes that oleothorax (gomenol in either paraffin or olive oil) has definite value as a temporary measure. He says, "The rate of reëxpansion after the gas has been replaced by oil is immediately slowed down to such an extent that the lung and mediastinum have time to accommodate themselves to the changing conditions." Matson (13) believes that oleothorax is a safe procedure and one which should be tried in these cases. We have had no experience in the use of oleothorax, and hesitate to recommend it. There does, however, seem to be some danger

in its use, since occasionally, when injected into the pleural sac, a severe reaction is produced by the oil.

It may be found that, when the lung has reëxpanded and become adherent to the chest-wall, an old cavity has reopened, or that phrenic interruption has not controlled a constantly retracting mediastinum and trachea: then thoracoplasty may be required. Reopened cavities, with subsequent return of bacilli in the sputum, will prove both dangerous to the patient from reinfection, and to the people with whom he lives and comes in contact. Therefore, even though thoracoplasty is a more drastic procedure and carries a greater risk, one should not hesitate to recommend it when more conservative remedies, like those listed above, have failed to give satisfactory results.

A brief report of 5 cases, accompanied by photographic X-ray films illustrating some of this work, follows:

Cases

1: J. D. M., male, aged 31, admitted to Blue Ridge Sanatorium, March 9, 1930. Physical examination and X-ray on admission disclosed a far-advanced case of tuberculosis, and tubercle bacilli were found in the sputum. In the right lung the upper and middle lobes showed an old fibrocaseous involvement with a cavity, 3 cm. in diameter, just below the clavicle. In the left lung there was light infiltration in the upper lobe. The patient's finances were limited, and it was necessary to shorten his stay in the Sanatorium as much as possible. His local and constitutional symptoms were moderate, and he was running about a half-degree of fever in the afternoon. Two months after admission, artificial pneumothorax was begun on the right. Many pleural adhesions were found, but, by giving frequent refills of air and using fairly high intrapleural pressure, the cavity was closed, and about 60 per cent of the lung compressed, which produced satisfactory therapeutic results. After a period of two and one-half years of collapse, the refills had to be discontinued because of obliteration of the pleural space by adhesions. Figure 1a shows the extent and type of disease, with cavitation in the upper and middle lobes of the right lung before compression was started. Figure 1b shows reëxpansion after two and one-half years of collapse, with nothing in the lung except some residual fibrosis in the region where the excavation formerly was located. It has now been three years since collapse treatment was discontinued, and the patient has been working two and one-half years of that time at his former occupation as travelling salesman. He seems to be in splendid physical condition and is apparently well clinically.

2: T. P. M., female, married, aged 23, admitted to Sanatorium, March 15, 1932, with far-advanced tuberculosis and tubercle bacilli in her sputum. In the

right lung there was a small amount of infiltration in the lung field, just off the root zone, and a small thin-walled cavity in the 2nd interspace. The greater part of the left lung was involved by consolidation and definite cavity-formation just below the clavicle. Both local and constitutional symptoms were pronounced, and the patient's temperature was 100° to 101° in the afternoon. Soon after admission, pneumothorax was started on the left side, and this was continued for two months with little or no result. As will be seen from figure

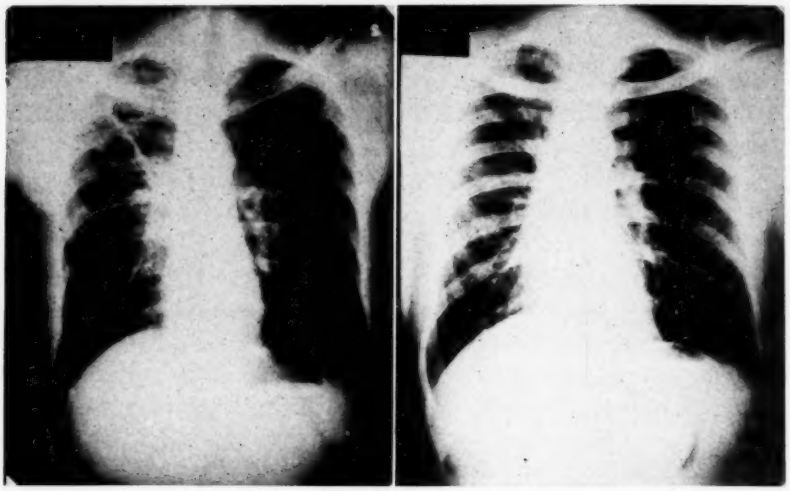

Fig. 1a Fig. 1b

CASE 1

Fig. 1a. Shows extensive tuberculous involvement in the upper and middle lobes of the right lung, with a 3-cm. cavity just below the clavicle. Slight involvement in the left. Tubercle bacilli in the sputum.

Fig. 1b. The same case, showing condition of the right lung on reëxpansion after two and one-half years of collapse by pneumothorax. Only residual fibrosis where cavity was formerly located. Sputum negative. No symptoms and patient apparently well and working.

2b, there was a large adhesion, which held open the cavity and which would not allow the lung to be compressed. This adhesion was cut, and, as will be seen from figure 2c, complete compression was obtained and the cavity closed. The sputum immediately became free of tubercle bacilli, and the patient has shown steady improvement since. Also, as will be noted from the X-ray films, the disease which was present in the right lung has improved and the small cavity has healed. Collapse treatment is being continued because there has not been sufficient time for the cavity to heal.

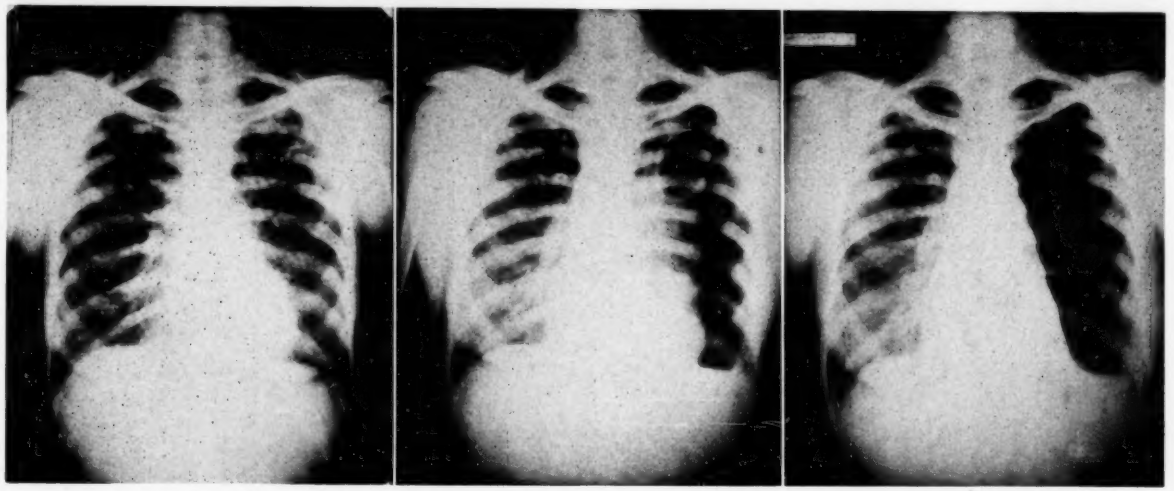

Fig. 2a Fig. 2b Fig. 2c

CASE 2

Fig. 2a. Before pneumothorax. Extensive tuberculosis in the greater part of the left lung, with consolidation and a large thin-walled cavity in the upper lobe. Light infiltration in right lung with small cavity in the 2nd interspace. Tubercle bacilli in the sputum.

Fig. 2b. Same case after pneumothorax was begun. Note cavity being held open by adhesions. The sputum continues positive. A trace of fluid is present in the base.

Fig. 2c. Same case after internal pneumonolysis. Cavity closed, and the lung is completely collapsed. Sputum negative, and the small cavity in the right replaced by fibrosis. Pneumothorax being continued. Patient is symptom-free. The lung was perhaps too tightly compressed at the time the film was made.

3: D. L. M., female, aged 26, married and having one child, was first admitted to the Sanatorium, March 23, 1930, and discharged October 18, 1930. She had a moderate case of tuberculosis in the left upper lobe, but tubercle bacilli could not be found in her sputum. She improved rapidly, and the lesion showed some retrogression, but she thought that she could get along well at home with her treatment and insisted on leaving the Sanatorium. On June 17, 1931, eight months after discharge, she was again admitted. At that time she was found to have a more extensive lesion in the left lung, with a thin-walled cavity, and tubercle bacilli in her sputum. Her symptoms as a whole were fairly slight, but, since she had a poor appetite and would not gain weight, it seemed advisable, one month after her second admission, to compress the left lung. This was done, but small pleural adhesions were found, which would not permit more than a 65 or 70 per cent compression; however, this was sufficient to render her sputum negative and to enable her to improve rapidly. After eighteen months of collapse, the patient insisted on going home. As an experienced physician for administering pneumothorax was not available for refills and continuing the collapse, the lung was allowed to reëxpand. Figure 3b shows reëxpansion of the lung with the cavity apparently closed. Eight months after discharge the patient had what was diagnosed as "influenza"; and, following this, she returned for a check-up of her chest condition, and, as will be noted from figure 3c, the old cavity had reopened and, in addition, there had developed in the lower lobe on this side a fairly marked tuberculous pneumonia. It is quite obvious in this case that the left lung was allowed to reëxpand too soon. Had collapse been continued for two to three years this patient would no doubt have received first class clinical results.

4: F. H. C., female, aged 17, was admitted to Sanatorium, November 12, 1929. She was transferred from another sanatorium, where she had been under treatment for about two months. On her admission to that institution, she was found to have a fairly heavy infiltration in the upper lobe of the left lung, with some slight cavity-formation. There was also a slight amount of infiltration in the upper lobe of the right lung. She had tubercle bacilli in her sputum, and, in order to control haemoptysis, compression therapy on the left was started. When she came to us the lung was in a fair state of compression, but tubercle bacilli were still present in her sputum. Pneumothorax was pushed to the point of complete collapse of the left lung. Steady improvement was made, and the disease in the right lung gradually disappeared; so, in the summer of 1931, after approximately two years of collapse treatment, she was admitted to our Training School for Nurses. She went through this course for two years with continued improvement. About the time she had completed the nurses' course, she stated one day that her left lung did not feel right and seemed as though she was breathing from it. Up to this time she had been

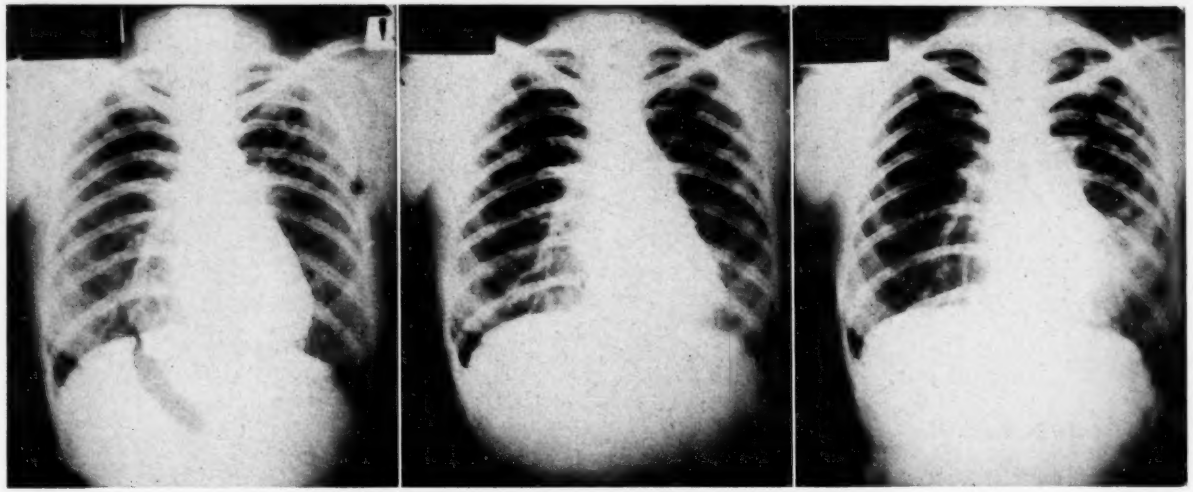

Fig. 3a Fig. 3b Fig. 3c

CASE 3

Fig. 3a. Before pneumothorax. Heavy infiltration in the left upper lobe with a thin-walled excavation in the 1st interspace. Tubercle bacilli in the sputum. Anorexia present.

Fig. 3b. Same case, showing left lung after reëxpansion. Was compressed only eighteen months. Cavity closed, and the sputum negative. Patient free from symptoms and returned to her home.

Fig. 3c. Same case seven months later, following influenza, when she returned to the Sanatorium with the cavity in the left lung again open and much larger and an area of tuberculous pneumonia in the lower lobe. Tubercle bacilli again present in the sputum, and symptoms pronounced. This case should have remained compressed for a period of at least four years. An attempt to recollapse the lung was made, but unsuccessfully because of pleural adhesions, and a phrenic avulsion was done. A thoracoplasty may be necessary to produce lasting results.

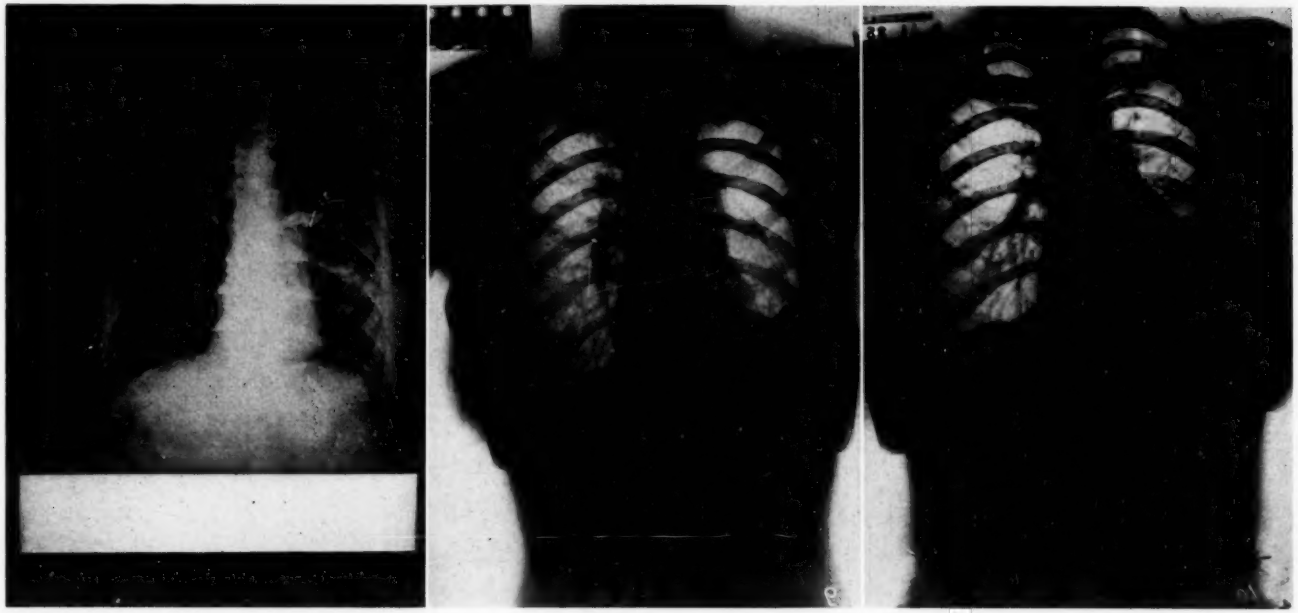

Fig. 4a Fig. 4b Fig. 4c

CASE 4

Fig. 4a. Before pneumothorax. Heavy infiltration in the left lung, with consolidation and slight cavity-formation in outer root zone. Tubercle bacilli in the sputum. Collapse instituted to control haemoptysis.

Fig. 4b. Same case after pneumothorax. Upper lobe completely collapsed, but lower lobe shows some expansion. Sputum negative. No symptoms. Patient working as a pupil nurse.

Fig. 4c. Same case, showing left lung reëxpanded after four and one-half years of compression. The lung looks normal, except for slight fibrous tissue-formation in the upper lobe. No complications: trachea and mediastinum in position. Sputum negative, and no symptoms. Patient is working steadily and appears well.

getting 300 to 350 cc. of air every fourteen days, and was fluoroscoped periodically which revealed a good compression. At this point the screen showed the lower lobe of the lung to be completely expanded and adherent to the chest-wall. In spite of the attempt to recollapse the lung, it continued to expand until there was no air in the pleural space. Figure 4c, taken after reexpansion, shows complete healing of the lung. This case was kept compressed between four and four and one-half years, which seemed to be satisfactory. In addition to this point, another interesting thing was the sudden absorption of air and the almost complete reëxpansion of the lung without the knowledge of the patient or the physician. This girl is now working, and appears to be well.

5: R. S. N., male, aged 49, admitted to the Sanatorium, November 19, 1931, with far-advanced tuberculosis of the lungs complicated by marked tuberculous involvement of the larynx, as well as tuberculous enterocolitis, and with sputum heavily laden with tubercle bacilli. An old fibrocaseous involvement was found occupying almost the entire right lung, with consolidation and a large thick-walled excavation in the upper lobe. Slight fibrocaseous involvement was present in the upper left. Both local and constitutional symptoms were marked, with temperature of more than 100° every afternoon. Just after admission, compression treatment was started on the right side. A few pleural adhesions were found, which did not materially interfere, but, due to the thick, rigid walls of the cavity, difficulty was experienced in trying to compress it. Large amounts of air injected under fairly high intrapleural pressure finally closed the cavity as will be noted from figure 5b. The patient's symptoms gradually improved and eventually disappeared, and the complications healed. However, after maintaining this high intrapleural pressure for some time, the patient began to have paroxysms of coughing, and this became so annoying that we had finally to discontinue compression. So much atelectasis had taken place from the tight compression that the upper lobe would not reëxpand, and, as will be seen from figure 5c, the trachea and mediastinal structures were drawn to this side. The patient's cough, while somewhat better after partial reëxpansion, is still a disturbing factor. We have just had the phrenic-crushing operation performed, and hope, by elevation of the diaphragm on this side, to push the lung up and fill in the vacant upper thoracic space, thus permitting the trachea and mediastinal structures to resume their normal positions. The operation has not been done long enough to tell just what the results are going to be. However, if it is not effectual, then an upper thoracoplasty will be advised.

CONCLUSIONS

An attempt has been made to evaluate the various points which should be considered before terminating artificial pneumothorax. Under

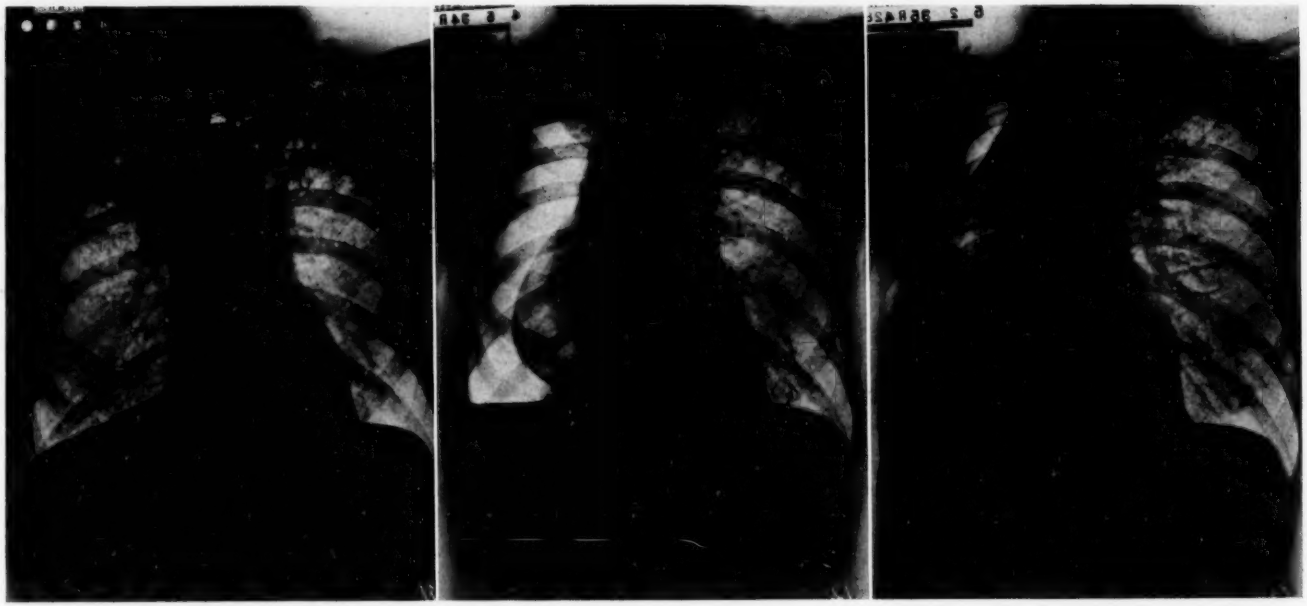

Fig. 5a Fig. 5b Fig. 5c

CASE 5

Fig. 5a. Before collapse: note marked disease in the right lung with a large thick-walled excavation below the clavicle. Some disease in left upper lobe. Innumerable tubercle bacilli in sputum, and marked local and constitutional symptoms.

Fig. 5b. Same case, showing complete collapse of right lung, and the cavity finally closed under high intrathoracic pressure. Small amount of fluid present. Sputum negative, and symptoms better.

Fig. 5c. Same case, showing right lung in a partial state of reëxpansion. Pressure symptoms so pronounced that refills had to be discontinued. Note lack of reëexpansion due to atelectasis in upper thorax and the displacement of trachea and heart to this side. Phrenic operation just performed in the attempt to correct this deformity.

"Undesirable Reëxpansion" there is a discussion of several conditions which may arise and cause a premature termination of collapse. These are dense obliterating pleural adhesions, pleural effusions and sudden absorption of air from the pleurae, named in the order of frequency. These may be unavoidable, and valuable time should not be lost by continuing refills when the desired therapeutic results are not being obtained. Phrenic interruption, internal pneumonolysis, or thoracoplasty should be considered.

Reactivation of an old lesion or the development of new disease in the contralateral lung is considered to be the most common cause for having to discontinue collapse. By keeping patients at complete bed-rest and avoiding overcollapse (not over 50 to 60 per cent), and giving frequent refills and small amounts of air each time, many of these cases may be continued indefinitely with benefit to both lungs.

Under "Voluntary Reëxpansion," consideration is given to the following conditions before permitting expansion: Extent and character of the pathological process in the lung before compression; clinical course of the disease before collapse; constitutional condition of the patient at the time; duration of period since sputum has been free from tubercle bacilli; economic status of the patient; and a general review of the indications for collapse therapy in the particular case. A red-cell sedimentation rate may be helpful in determining whether or not there is activity in the collapsed lung. While the rule cannot and should not be strictly adhered to, it may be said that fairly light infiltrations, but diffuse throughout a lobe and without cavitation, should remain collapsed for a period of two to three years; heavy consolidations, with or without thin-walled cavities, should stay collapsed for at least four years; and dense fibrocaseous lesions with thick-walled cavities will require five, six or more years to heal under compression.

Some attention has been given to complications which may arise after reinflation, such as fibrosis and atelectasis, causing displacement by pulling the mediastinal structures to the affected side. Suggestions as to their prevention, and to the correction of them if they develop, are given.

No case of pneumothorax should be discontinued until the X-rays and clinical course of the patient prior to the institution of pneumothorax have been carefully reviewed.

The results on 59 cases of pneumothorax having internal pneumonolysis are reported.

Five cases of artificial pneumothorax are reported which are illustrated by photographic X-ray films. Four of these cases are shown after reëxpansion of the lung. One had a relapse due to too early termination of collapse. One had involuntary reëxpansion due to too rapid an absorption of air from the pleural sac, but good results were obtained. One was voluntarily permitted to reëxpand after two and one half years of collapse, and the cavity was healed and splendid results obtained. The fourth and last case, after two and one-half years of collapse, had to be allowed to reëxpand due to pressure symptoms. Marked atelectasis was present and complete reëxpansion would not take place: therefore, a phrenic interruption operation was performed in the attempt to fill in the "vacant space" in the upper thorax and allow the trachea and mediastinal structures to return to their normal position. The fifth case is still under compression, and illustrates the value of internal pneumonolysis in selected cases.

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A NEW ARTIFICIAL-PNEUMOTHORAX APPARATUS

ROBERT G. BRAMKAMP[1]

Many different devices for the administration of artificial pneumothorax have been described. References to some of the early, recent, and representative intermediate outfits are appended. The arrangements in most common use at present are the Cutler-Loving, Davidson, Wooding, and modifications of the original Robinson apparatus.

The apparatus to be described offers nothing new in principle, but seems to have several desirable features. The whole apparatus when assembled costs less than one-third of the current commercial outfits, and requires only materials that are easily obtainable. Recent additions to the commercial products:—marker for fluid-level in bottles, manometer-traps, pressure-bulb, air-washer and filter, are included in this apparatus.

The illustrations are self explanatory (figures 1 and 2). Twelve-hundred-cubic-centimetre Pyrex bottles are used; the tubing may be either Pyrex or softer glass. For administering the gas, two stopcocks are used: one is between the two bottles, the other is a three-way cock connecting the gas bottles with either the chest tube or the manometer.

Some points in construction and use of the apparatus:

1: The all-glass gauge system with the safety bulb renders it almost impossible for anything but gas to be introduced into the pleural cavity, and affords completely visible change in the fluid volumes. The gas may be washed and filtered if desired by inserting between the lower bottle and the three-way way cock a wash bottle filled with the washing fluid and a drying tube filled with absorbent material.

2: Disassembling the apparatus for emptying or filling the bottles is made unnecessary by the lower openings in them.

3: Lubricated glass stopcocks are less liable to leak air than metal or hard rubber ones.

4: Filling, emptying, adjusting and cleaning the gauge, difficult in most instruments, is easily done by means of the stopcock at the bottom.

5: Rarely, in spontaneous pneumothorax with valve-action causing progressive

[1] Banning, California.

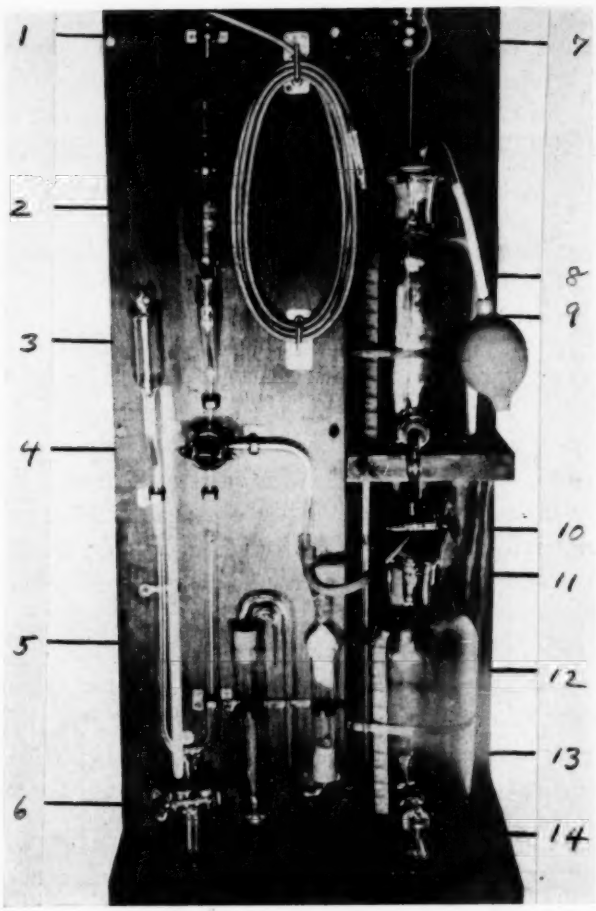

FIG. 1. THE APPARATUS

1. Tube to pleural cavity
2. Trap
3. Trap for filling manometer
4. Three-way stopcock connecting chest with either manometer or gas system
5. Manometer
6. Stopcock for adjusting manometer fluid-level
7. Thistle tube for filling; also to act as pressure regulator
8. Aspirator bottle, 1200 cc. ("one litre")
9. Pressure-bulb, for increasing rate of flow if desired
10. Stopcock controlling flow from upper to lower bottle
11. Tube connecting bottles with gauge-system
12. Marker for fluid-level in bottle
13. Tubes for washing and filtering the gas; may be connected between lower bottle and gauge if desired
14. Stopcock for emptying lower bottle.

increase in intrathoracic pressure, it becomes desirable to remove a measured quantity of air from the pleural cavity. This is accomplished by connecting

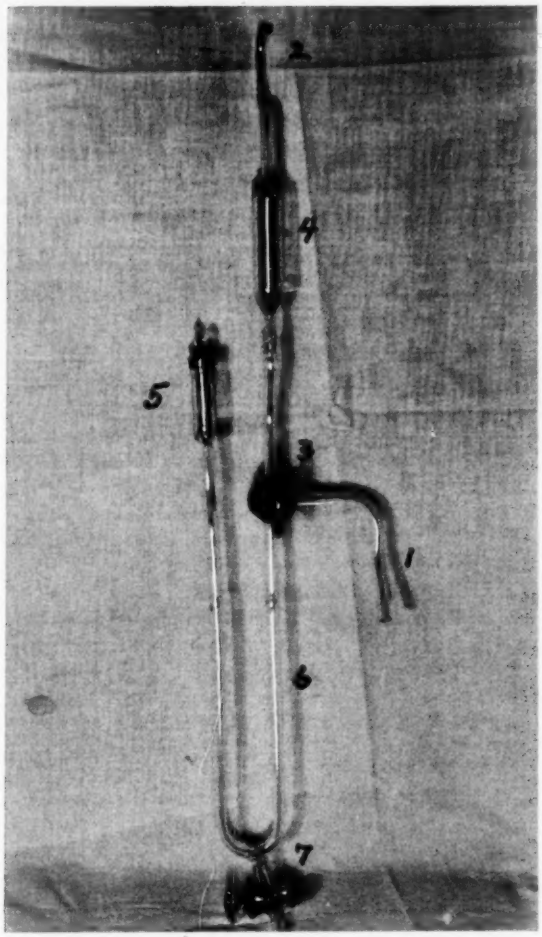

FIG. 2. THE MANOMETER SYSTEM

1. To bottles
2. To chest
3. Three-way stopcock
4. Trap
5. Trap
6. Manometer
7. Stopcock for adjusting manometer fluid level

the pleural cavity with the apparatus in the usual manner and allowing water to flow from the lower stopcock in the lower bottle until the desired quantity of gas has been aspirated.

6: The thistle tube, used for filling the upper bottle, acts also as a safety valve when the pressure-bulb is used to give more rapid flow of gas, and the pressure at no time can be greater than the height of a column of water equal to the distance between the top of the tube and the level in the lower bottle.

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THE INTENSITY OF THE TUBERCULIN REACTION AND FREQUENCY OF DEMONSTRABLE TUBERCULOUS LESIONS

As Observed in Kingston, Jamaica[1]

C. W. WELLS AND H. H. SMITH

Sensitized tissue brought in contact with tuberculoprotein as a rule results in a definite reaction, which has long been recognized and designated as a tuberculin-positive reaction. Variation in the degree of this reaction has been noted, but with the cutaneous test other factors than the degree of sensitization might have been operative. With the advent of the intracutaneous tuberculin test extraneous factors have been largely excluded and the test becomes more dependable. Investigations have been conducted by various workers in an attempt to interpret the meaning or importance of the variations in intensity seen in positive reactions. It is generally recognized that a positive tuberculin reaction indicates that the body cells have previously been brought into intimate contact with tubercle bacilli, although a negative reaction does not necessarily mean the absence of such contact.

The earlier studies of this problem were attempts to connect the more marked reactions with the occurrence of active tuberculosis in the individual, on a quantitative basis, by establishing a critical threshold with respect to the quantity of tuberculin employed. It was believed that a point might be reached in the dilution of tuberculin which would definitely exclude the majority of negative reactors from all suspicion of having tuberculosis. This point of view was advanced by Atsatt (1) who tested 85 tuberculous cases and 126 nontuberculous individuals, employing a 1 to 10,000 dilution of O.T. intracutaneously. He reported that 92 per cent of the tuberculous cases gave a positive reaction, while 90 per cent of the nontuberculous individuals were negative. As a result of this study, Atsatt advanced the hypothesis that a critical threshold might be established, suggesting that reactions to dilutions of O.T. above the threshold might be considered as usually indicative of active tuberculosis.

[1] These studies were conducted with the support and under the auspices of the International Health Division of The Rockefeller Foundation, in coöperation with the Jamaican Government Medical Department.

Blair and Galland (2) were impressed with Atsatt's findings, and in support of them reported their results, using a dilution of 1 to 100,000 of O.T. Ninety per cent of 121 tuberculous cases gave a positive reaction. Several of the negatives were moribund; 92 per cent of 350 nontuberculous individuals were negative to the test.

King (3) applied the tuberculin test to 225 adults, using a dilution of 1 to 20,000. His cases were suffering from a wide variety of disorders. The results of the tuberculin test were in accord with the clinical diagnosis in 90 per cent of the cases. This investigator concluded that "the quantitative factor or measure of the degree of tuberculin hypersensitivity as a guide to the activity of a tuberculous focus has been sadly neglected."

Stewart (4) studied the tuberculin reaction in 188 children between 8 and 17 years of age, and found little difference in the extent of the skin reaction between positive cases and those with latent or without demonstrable lesions. He concluded that his results "failed to justify the suspicion that children with large and intense intracutaneous reactions harbour more intensive pathologic changes or have more active primary tuberculous lesions than do other children who are less sensitive to tuberculin." Unfortunately, only 21 of the 188 children in this series presented negative X-ray chest findings, the remaining children having active, latent or suspicious findings.

The entire question of the relation between the intensity of the tuberculin reaction and the presence of demonstrable X-ray lesions has received further investigation by Opie and his associates (5). Using a concentration of 0.01 mgm. of tuberculin, 299 children between 5 and 19 years of age were tested and received X-ray examinations of the chest. Results are shown graphically in chart 1"B" and tabulated in table 1. "With a negative tuberculin reaction, 17.3 per cent have lesions characteristic of latent or manifest tuberculosis . . . with positive reactions, increasing intensity of reaction is associated with gradually mounting frequency of recognizable tuberculous lesions." These investigators found the following incidence of lesions with respective tuberculin reactions:

	per cent
No reactions to 1.0 mgm	17.3
Positive to 0.1 and 1.0 mgm	28.2
One plus positive to 0.01 mgm	37.9
Two, three and four plus to 0.01 mgm	55.9

They further concluded, "the probability of grave tuberculous infection increases with the severity of the tuberculin reaction."

In a more extensive study, Opie, *et al.* (6), 1,321 children between 5 and 19 years of age were tested and X-rayed. Of those positive to 0.01 mgm.,

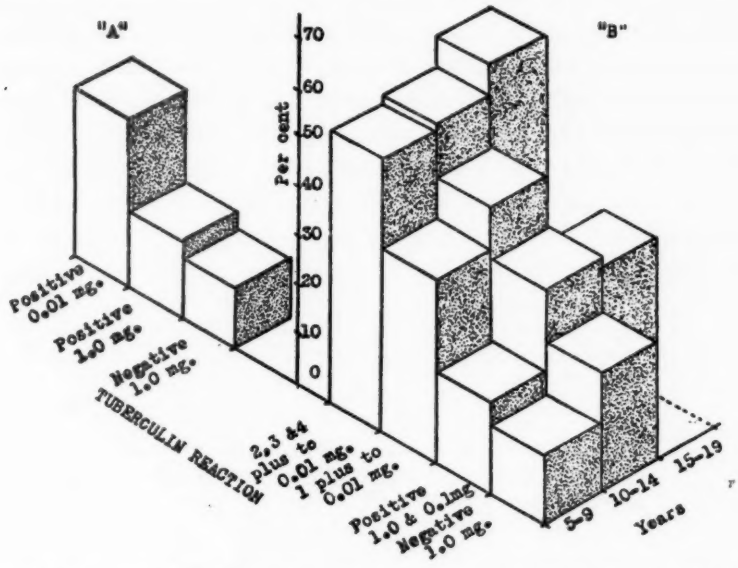

CHART 1. Per cent X-ray demonstrable lesions in relation to the intensity of the tuberculin reactions. "A," Opie, *et al.* (6); for ages 5 to 19 years combined. "B," Opie and McPhedran (5).

TABLE 1

X-ray findings in relation to the intensity of the tuberculin reaction (from Opie and McPhedran, American Review of Tuberculosis, xiv, 1926)

AGE	NUMBER TESTED AND X-RAYED	ONE PLUS TO 0.01 MGM.			TWO, THREE AND FOUR PLUS TO 0.01 MGM.			POSITIVE TO 0.1 AND 1.0 MGM.			NEGATIVE TO 1.0 MGM.		
		Number Positive and X-rayed	Demonstrable X-ray Lesions	Per cent X-ray Lesions	Number Positive and X-rayed	Demonstrable X-ray Lesions	Per cent X-ray Lesions	Number Positive and X-rayed	Demonstrable X-ray Lesions	Per cent X-ray Lesions	Number Negative and X-rayed	Demonstrable X-ray Lesions	Per cent X-ray Lesions
5–9	142	16	6	37.5	51	28	54.9	16	3	18.7	59	8	13.6
10–14	132	11	5	45.5	63	35	55.6	17	6	35.3	41	10	24.4
15–19	25	2	0	0.0	13	8	61.5	6	2	33.3	4	0	0.0
Total.....	299	29	11	37.9	127	71	55.9	39	11	28.2	104	18	17.3

33.6 per cent presented recognizable X-ray lesions; 15 per cent of those positive to 1 mgm. showed similar findings, and 12.1 per cent of those

negative to 1 mgm. presented X-ray lesions. These findings for all ages combined are shown graphically in chart 1"A."

. The conclusion that one may expect an increase in the per cent of demonstrable pulmonary lesions with an increase in the severity of the tuberculin reaction is dramatically shown by these results, especially when presented graphically. The findings in the 15- to 19-year group are less significant because of the relatively few individuals examined in this class. A further point of interest is the definite increase in the per cent of lesions for each severity of reaction in the group 10 to 14 years over the results obtained for the age-group 5 to 9 years. This is a logical finding, since older individuals, living under similar environmental

TABLE 2

X-ray findings in relation to the intensity of the tuberculin reaction for Kingston survey areas

AGE	TOTAL NUMBER TESTED AND X-RAYED	ONE PLUS TO 0.01 MGM.					TWO, THREE AND FOUR PLUS POSITIVE TO 0.01 MGM.					POSITIVE TO 1.0 MGM.					NEGATIVE TO 1.0 MGM.				
		Number Positive and X-rayed	X-ray Findings				Number Positive and X-rayed	X-ray Findings				Number Positive and X-rayed	X-ray Findings				Number Negative and X-rayed	X-ray Findings			
			Latent	Pulmonary Tuberculosis	Total	Per cent Positive		Latent	Pulmonary Tuberculosis	Total	Per cent Positive		Latent	Pulmonary Tuberculosis	Total	Per cent Positive		Latent	Pulmonary Tuberculosis	Total	Per cent Positive
0–9	884	212	12	1	13	6.1	128	18	0	18	14.1	174	2	1	3	1.7	370	2	0	2	0.5
10–14	412	162	11	0	11	6.8	120	17	0	17	14.2	74	1	0	1	1.4	55	0	0	0	0.0
15+	3610	1525	117	23	140	9.2	1497	144	37	181	12.1	460	21	3	24	5.2	128	5	2	7	5.5
Total...	4906	1899	140	24	164	8.6	1745	179	37	216	12.4	708	24	4	28	4.0	553	7	2	9	1.6

conditions as younger persons, have additional opportunity for exposure to infection, at least to the degree represented by the additional years in their age. This exposure should produce some increase in infection with resultant demonstrable X-ray lesions.

In the course of a tuberculosis survey in Kingston, Jamaica, B. W. I., conducted from 1931 to early in 1934, 4,906 individuals were tuberculin-tested and received chest X-ray examinations. Fortunately for the purpose in hand, 553 negative reactors to 1 mgm. of tuberculin were included in those X-rayed. Compared to the Philadelphia studies, the prevalence of demonstrable lesions in the Jamaica series is considerably lower. Nevertheless, when compared to the intensity of the tuberculin reaction, the relationship is striking and a significant correlation is

demonstrated. The results of the Kingston study are given in table 2 and shown graphically in charts 2 and 3.

Combining latent and manifest lesions (chart 2), a marked increase was found in the per cent of lesions for all ages, with increase in severity of reaction to tuberculin, this correlation being more pronounced in the age groups under 14 years of age. For the age-group 0–9 years, 0.5 per

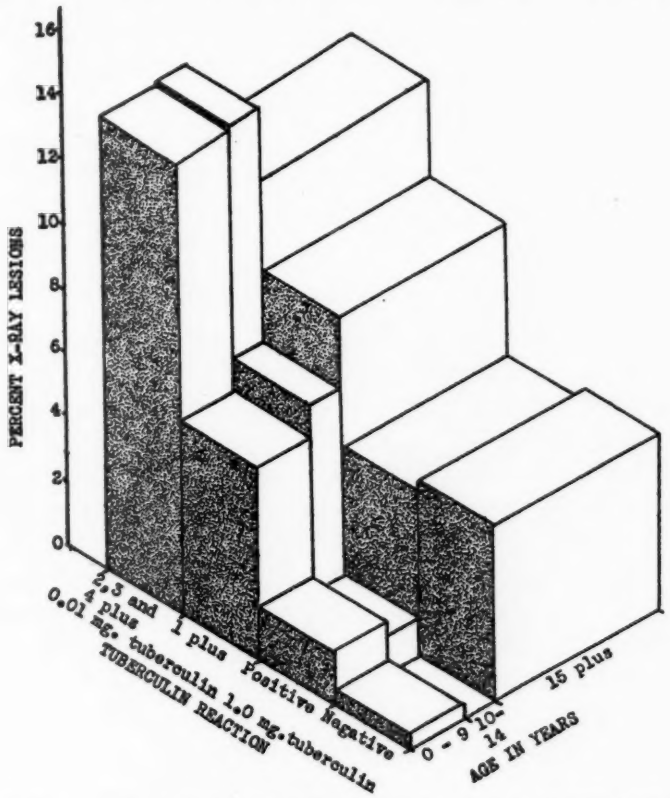

CHART 2. Per cent X-ray demonstrable lesions in relation to the intensity of the tuberculin reaction, by age. Kingston, Jamaica.

cent of negative reactors presented lesions, rising to 14.1 per cent for two-, three- and four-plus reactors to 0.01 mgm. of tuberculin. In the age-group 10–14 years, no lesions were found among negative reactors, while the two-, three- and four-plus reactors to 0.01 mgm. showed 14.2 per cent lesions. Among individuals 15 years of age and over, 5.5 per cent of the negative reactors presented lesions, rising to 12.1 per cent

for the two-, three- and four-plus reactors to 0.01 mgm. That the increase in the proportion of lesions with severity of the tuberculin reaction is significant has been determined by applying the method of Yule to the data. Testing the negative and positive reactors to 1 mgm. against the positive reactors to 0.01 mgm. resulted in $X^2 = 67.7$, which gave a P value of .0000.

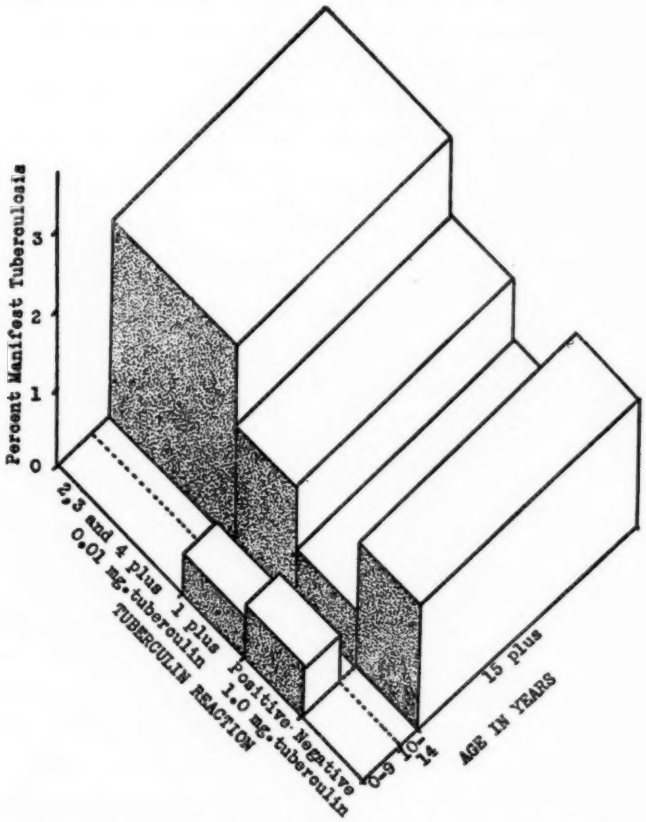

CHART 3. Per cent manifest pulmonary tuberculosis in relation to the intensity of the tuberculin reaction, by age. Kingston, Jamaica.

Little or no difference was found in comparing the results obtained in the 0–9 year and 10–14 year groups. While in the 15-plus year group, a considerably higher per cent was found for three of the reactions when compared to the younger ages. The relatively low prevalence of lesions for the entire group of individuals probably accounts, in large measure, for the slight differences between the two younger age-groups.

Chart 3 shows the distribution of manifest pulmonary tuberculosis according to the intensity of the tuberculin reaction. An increase was found in per cent of lesions, with increase in the severity of the tuberculin reaction for ages 15 years and over. The significance of the distribution of lesions for all ages is indicated by an X^2 of 9.98 and a P value of 0.002, obtained by Yule's Fourfold Method, grouping positive reactors to 0.01 mgm. of tuberculin against those tested with 1 mgm.

Mention should be made of the amount of demonstrable lesions, both active and latent, in individuals who were negative to 1 mgm. of tuberculin. This finding is not unusual and is well recognized. Opie and McPhedran (5) found 17.3 per cent of lesions among negative reactors, while in our series 1.6 per cent of lesions was found in the group of negative reactors. Two of the individuals in this group were suffering from far-advanced active disease.

DISCUSSION AND CONCLUSION

In recent years, interest has been shown in the varying degrees of severity of reaction to the tuberculin test. The first study of the problem employing the intracutaneous test was that reported by Roemer and Joseph (7). These investigators applied the test to a series of guinea pigs in which tuberculous infection of all grades had been produced. They reported a definite correlation between the degree of infection and the severity of the tuberculin test, using high dilutions of tuberculin. In recent years investigations of this phenomenon, to which reference has been made, have been concerned with efforts to associate the more pronounced and severe reactions to the intracutaneous tuberculin test with active tuberculosis, on a quantitative basis; the idea being advanced that a given dilution of tuberculin might be established which would more or less definitely exclude, in the majority of negative reactors, the possibility of tuberculosis.

As pointed out by Rich and McCordock (8) a negative reaction does not absolutely exclude active or far-advanced tuberculosis, even when relatively enormous doses of tuberculin are employed. It is recognized that 3 to 5 per cent of cases of miliary tuberculosis fail to react to average doses of tuberculin; that sensitization diminishes or disappears during certain intercurrent infections, as well as other conditions noninfectious in nature which may disturb the normal condition of the skin, and that, finally, in the far-advanced and moribund tuberculous cases, allergy is definitely decreased.

This report confirms in part the previous studies of this problem, but

does not attempt to determine a critical threshold in the dilution of tuberculin, except in accepting the dilutions generally employed in making routine tuberculin tests. Our study applied the test, not to selected groups of suspicious tuberculous individuals, but to a random sample of the population. Our results and those of Opie and his associates are thus comparable for individuals in the school-age groups, both studies providing confirmation for the conclusions drawn therefrom. Of additional interest is the fact that the studies of Opie and his associates were conducted in a northern city, while the Kingston data applies to the results obtained under tropical conditions and largely in the colored race.

This report reveals a definite and significant upward trend in the per cent of tuberculous infection, both latent and manifest, with increasing severity in the tuberculin reaction among 4,906 individuals of all ages. In the 0–9 year age-group, the per cent of infection ranged from 0.5 per cent for negative reactors to 1 mgm. to 14.1 per cent in the two-, three- and four-plus reactors to 0.01 mgm. In the 10–14 year age-group no lesions were found in negative reactors and 14.2 per cent of lesions in the two-, three- and four-plus reactors. For all ages over 15 years, 5.5 per cent of lesions were found in negative reactors and 12.1 per cent in those showing two-, three- and four-plus reactions to 0.01 mgm.

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BRONCHOGENIC CARCINOMA

A Case Report[1]

J. K. MILLER

The early X-ray findings in main-bronchus cancer often fail to show the primary mass of which the stenotic tendency, however, may result in such processes as atelectasis, bronchiectasis, and abscesses which are discernible and form the basis for the diagnosis. Yet, these same manifestations can cast false clues. The following case illustrates this premise.

Clinical History

E. P., white, male, a dyer, 47 years old, was admitted, January 14, 1935, complaining of productive cough, dyspnoea, fever and chills, anorexia, mediastinal pains, and a loss of 18 lbs. in weight since the onset, November 1, 1934. Also, pain in the right flank had been noted for the past 4 weeks. In December he was hospitalized, and a thorough study, including X-rays of the chest, abdomen and genitourinary system, was made. He was referred to the Sanatorium with the diagnosis of suspected pulmonary tuberculosis.

Physical examination showed moderate emaciation, clubbing of the fingers diminution of breath-sounds throughout both lung fields, and bronchial breathing, with a few coarse râles in the right base. The liver was palpable, 5 cm. below the right costal margin.

X-ray examination: Chest (January 16, 1935): The right lung field showed scattered mottling of the productive type from the 1st rib to the diaphragm, most pronounced in the lower third; and the left, accentuated markings with slight mottling of the lower third of the field. *Chest:* (January 26, 1935): The right lung field showed a mottling from the clavicle to the 2nd rib; from there to the base a dense clouding was seen. The left lung was unchanged. The mediastinum was shifted to the right. *Chest:* (February 3, 1935): An immediate postmortem film showed in the right lung field a mottling in the 1st and 3rd interspaces. The lower third showed a triangular area of increased density, the base of which was toward the hilum. The left lung was unchanged.

Laboratory: The sputum was persistently negative. The red-cell sedi-

[1] From the State Sanatorium, Wallum Lake, Rhode Island.

FIG. 1

FIG. 2

FIG. 3

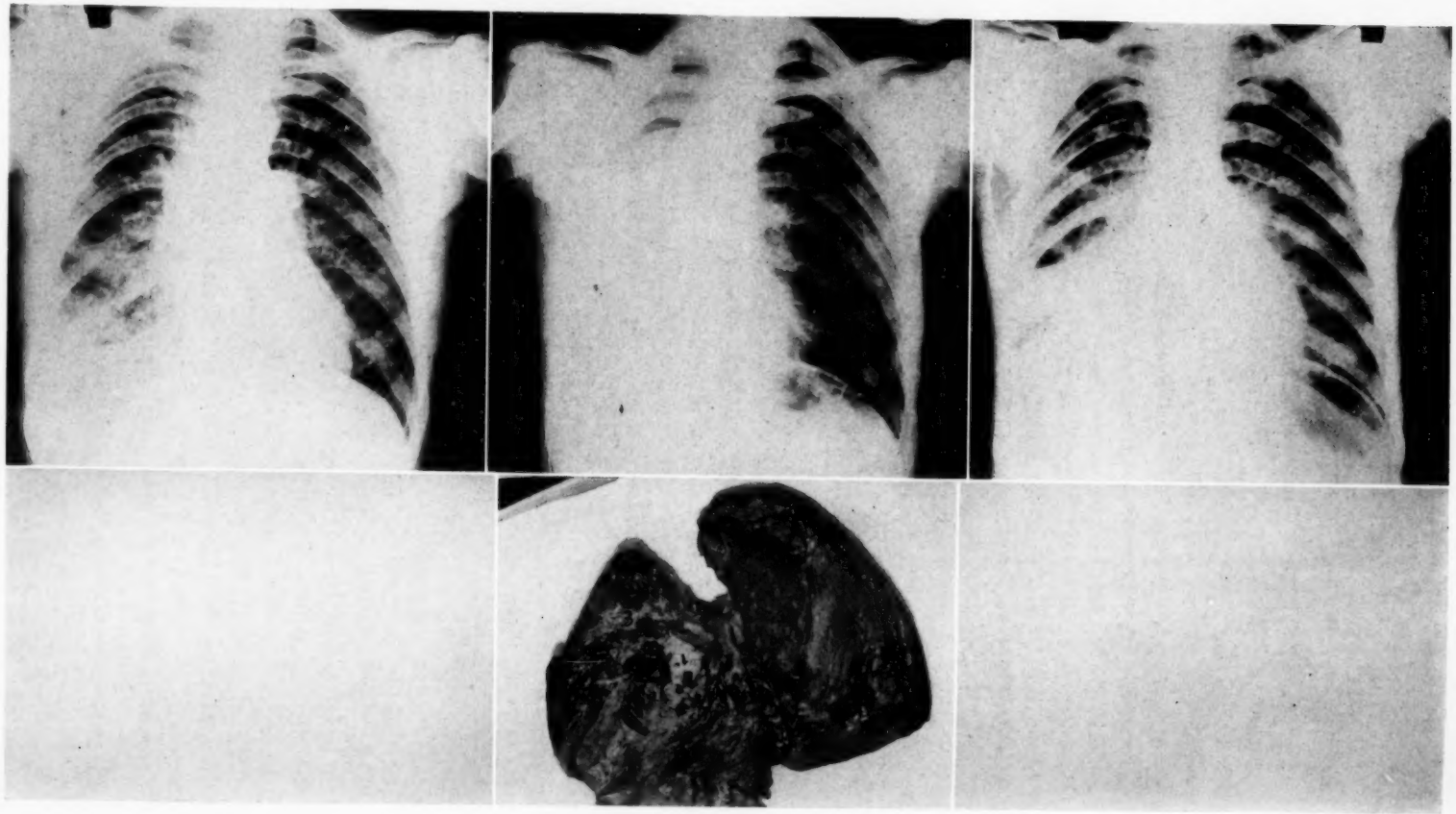

FIG. 4

mentation rate was 45 mm. in one hour, and 57 mm. the second hour. There was a leucocytosis of 15,000 with 6 per cent *stabs*, 71 per cent polymorphonuclears and 23 per cent lymphocytes.

Progress: The patient became steadily worse. The daily sputum output was from 90 to 130 gm.

Autopsy Findings

The upper and middle lobes of the right lung showed numerous minute abscesses scattered throughout the parenchyma. The interlobar septum of the middle and lower lobes presented an encapsulated empyema, with a capacity of 75 to 100 cc. The right lower lobe showed a moderate bronchiectasis and numerous abscesses, 0.5 to 1 cm. in diameter. The wall of the right bronchus was made up of an encircling mass, 1.5 cm. in thickness, at a point just beyond the bifurcation. The tissue was gray, and cartilaginous in consistency. The remainder of the bronchus and its branches presented a suppurative process. The left lung showed a moderate congestion along its vertebral border. The mediastinal nodes were enlarged. The pulmonary vessels were patent.

FIG. 1. Chest film of January 16, 1935, showing diffuse mottling of right lung.

FIG. 2. Chest film of January 26, 1935, showing the atelectasis of right lung.

FIG. 3. Chest film of February 3, 1935, showing shadow of interlobar empyema.

FIG. 4. Gross specimen of both lungs, showing the tumor mass surrounding the main bronchus (1), the empyema cavity (2) and the areas of abscesses (3).

In the anterior wall of the right auricle of the heart was found a metastatic nodule, 1 cm. in diameter, and a similar smaller nodule was seen in the left auricular appendage. Two small nodules were embedded in the wall of the left ventricle. The right kidney showed a necrotic tumor mass, 1.2 cm. in diameter, at its superior pole. The right adrenal had been replaced by a metastatic mass weighing 80 gm.

Microscopic examination of the primary tumor and its secondary colonies showed a bronchogenic carcinoma, epidermoid, grade II, R. R.

DISCUSSION

From the autopsy findings, it is observed that the initial mottling seen in the right lung field was due to the diffuse suppurative process of the lung in the form of miliary abscesses. The roentgenographic shadows cast by this pathological involvement suggested a tuberculous process and gave a false impression. The persistently negative sputum, however, deferred such an opinion, and an early death permitted autopsy studies to reveal the actual disease. The X-ray picture of atelectasis, mediastinal shift and bronchiectasis, which followed the initial impression, was

in accord with hilar cancer; although the neoplasm did not cast a sufficiently clear shadow to suggest its presence. All the confusion may be laid at the door of the process of miliary abscesses which preceded the subsequent characteristic manifestations of bronchostenosing tumors.

Bronchiectasis with its attendant suppurative processes is a frequent consequence of the stenosing main-bronchus tumors. Adler found that 36 of his 374 cases of lung cancer presented bronchiectasis. Rabin and Neuhof state that "the roentgen picture of main bronchus tumors is dependent upon the presence or absence of bronchostenosis. The typical evidence of atelectasis in bronchostenosing tumors requires no comment. When infection supervenes, the appearance is that of a pulmonary or pleural suppuration."

SUMMARY

A case of main-bronchus cancer is reported in which the first X-ray findings were those produced by a diffuse process of miliary abscesses of the upper and middle right lobes of the lung. This picture gave a false impression of a productive tuberculous lesion. The subsequent course was typical of a hilar growth. Any case over 40 years of age presenting a suggestive X-ray finding of suppuration warrants the serious consideration of malignant tumor of the main bronchus.

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THE USE OF THE BCG VACCINE AGAINST TUBERCULOSIS IN CHILDREN[1,2]

Eight Years' Experience

CAMILLE KERESZTURI AND WILLIAM H. PARK

The purpose of this study was threefold: namely, to find out from our own experience whether the use of the Calmette vaccine is free of harm to human beings; whether it is effective in the prevention of tuberculosis; and, finally, whether the good accomplished by it is great enough to warrant its use on a large scale as a public health measure. According to these three problems, we are presenting our material in three chapters.

CHAPTER I. IS THE BCG VACCINE HARMLESS?

After one year of animal experimentation by King, Park and their associates, on 400 to 500 guinea pigs, rabbits and some monkeys, it was felt that enough evidence had been accumulated by their own work to substantiate Calmette's claim that the BCG vaccine is harmless to animals even in very large doses, and that it causes a very definite immunity and can therefore be safely tried on human beings. According to the literature, the BCG vaccine is suitable for use by injection into human beings of any age provided they are free from tuberculous infection.

However, as the mortality rate of tuberculosis is different at various ages, we chose for vaccination a group in which the tuberculosis death-

[1] From the Department of Health, New York City.

[2] This work was financed by the Metropolitan Life Insurance Company, by the Department of Health of New York City, and, for a time, by the Milbank Memorial Fund. It was carried out at the Fifth Avenue Hospital, Babies Hospital, Harlem Hospital, Bellevue Hospital, Greenpoint Hospital, Long Island College Hospital and Sea View Hospital. The BCG staff consists of William H. Park, M.D., Director of the Staff; Camille Kereszturi, M.D., Chief Pediatrician; Milton I. Levine, M.D., Peter Vogel, M.D., David Hauptmann, M.D., Morris Siegel, M.D., Harold Rosenberg, M.D., Assistant Pediatricians; Margaret Sackett, R.N., Charge Nurse; Gertrude Richardson, R.N., Raynie Stebbins, R.N., Edith Marcus, R.N., Catharine Upton, R.N., Assistant Nurses; and Agnes Leach, Social Worker. We are especially grateful to Bela Schick, M.D., Herbert Edwards, M.D., Emil Bogen, M.D., and Eugene L. Opie, M.D., and Louis I. Dublin, Ph.D., for their kind help in several consultations.

rate is high, namely, children of tuberculous families who, with a few exceptions, were less than one year of age when they entered our study group. In keeping all the cases within a narrow age limit, we found it easier to draw statistical conclusions from our material. Although all our children are members of tuberculous families, in some instances the child never came in contact with the tuberculous source, when, for example, the tuberculous member was hospitalized during our whole observation time or died before contact with the child could occur. The children just mentioned were not suitable for testing the efficacy of the BCG vaccine; however, they were extremely valuable for testing whether the BCG vaccine is harmless or harmful for them. We have a group of 175 such BCG cases who, according to our knowledge, were not exposed to tuberculosis after vaccination. These cases were followed for different lengths of time from one month to eight years. With the possible exception of one case, no clinical tuberculosis developed in this group. On an average, all of them did as well as the controls. Fifteen died of some nontuberculous disease. Nine of these were autopsied and showed no tuberculous process. Bacteriological studies were carried out on six of the autopsied cases by Miss L. Mishulow in the Bureau of Laboratories, and in the organs of five no BCG or other types of tubercle bacilli were found. In the sixth patient, BCG bacilli were recovered. This case died of alimentary intoxication when he was six weeks old. At the age of one week he had been vaccinated orally with BCG. Autopsy did not reveal macroscopic or microscopic changes suggesting tuberculosis anywhere in the body. The BCG bacilli were found on culture in the mesenteric lymph nodes. However, guinea pigs and rabbits when inoculated with this culture failed to show tuberculous lesions which may be taken as evidence that the BCG bacilli failed to become more virulent from passage through the human body.

One of the nonexposed children who was vaccinated orally was counted by us as dying of tuberculosis. The study of this case has been given in a previous paper. Very briefly it was as follows:

Baby M. N. was a premature baby orally vaccinated within the first week of life. His mother died ten days after delivery of miliary tuberculosis. According to our information, the baby was never fed by the mother nor exposed to her. The child never did well and was always a feeding problem. Six tuberculin tests up to 1.0 mgm., chest roentgenograms and lung signs were negative. Finally, at the age of four months, the baby developed a severe alimentary upset, cough, chest signs, fever and general disseminated shadows

in the chest roentgenogram. The tuberculin test was still negative. The child died, but autopsy was refused. We considered this baby as a possible case of congenital tuberculosis infected by a mother who had miliary tuberculosis. However, it is possible that, unknown to us, this baby was exposed for a short time to the mother within the first ten days of life, or that he died of bronchopneumonia and not of tuberculosis. Whatever the cause of death might have been, we prefer, in making our statistics, to err against the BCG rather than for it. Therefore, we listed this baby as one dying of tuberculosis.

Another child, J. K., was intimately exposed to open tuberculosis from birth to $1\frac{1}{4}$ months of age. One week after the cessation of the exposure, the intracutaneous test to 10.0 mgm. O. T., physical examination and chest roentgenogram were negative and the child was intracutaneously vaccinated with BCG. Weekly tuberculin tests with 0.1 mgm. O. T. were negative. Four weeks after vaccination the child developed alimentary intoxication and died with clinical symptoms of bronchopneumonia. Autopsy was performed and caseating mediastinal lymph nodes and generalized miliary tuberculosis were found. The tuberculous involvement was more extensive than one would expect it to be if it developed after vaccination. Bacteriological study of the organs showed typical human tubercle bacilli identified by colony morphology. The baby was not exposed to known human tuberculosis after vaccination.

The probable interpretation of this case is that the human infection occurred before vaccination. The infant was in the incubation period of tuberculosis when vaccinated. The disease progressed so rapidly that there was no time for the child to become allergic either from the human or the bovine infection.

The conclusion to be drawn from this case is that if one wants to be sure not to administer the BCG vaccine to already infected children, one should follow the procedure of Walgren. He quarantines the children for three months from their tuberculous contacts prior to BCG vaccination in order to be sure not to vaccinate infants already tuberculous.

Unfortunately, we have no facilities to separate the child from the tuberculous contact safely, either before or after vaccination. Even if complete protection cannot be expected with our method of BCG vaccination, it is interesting to see how much effect BCG has against tuberculosis when used without prevaccination or postvaccination separation.

On the basis of our eight years' experience with these 175 nonexposed vaccinated children, we feel that BCG vaccination is free from danger

to children. We have had the same experience with 515 exposed BCG children. On the average, in some respects they did as well as the corresponding controls, and, in other respects, better. Four of them died of tuberculosis. All four were autopsied and studied bacteriologically, and tubercle bacilli of human type, characteristic by culture and animal inoculation, were recovered from their organs (of three out of four) which means that human tubercle bacilli and not the BCG caused their death. In the fourth case no tubercle bacilli were found.

We have further evidence of the harmlessness of the BCG vaccine in human beings. In order to see whether or not the BCG bacilli might become more virulent during their stay in the human body, we studied the virulence of bacilli recovered from the cold abscesses which sometimes occur in parenterally vaccinated children at the site of vaccination. The pus of thirty-one BCG abscesses was aspirated and cultured. BCG bacilli were obtained in 27 of the 31 instances. The stay of the bacilli in the human body varied from one to ten months. The cultures were identified as BCG cultures by colony morphology and inoculations into guinea pigs and rabbits. In none of the instances could an increase in virulence be determined.

The summary of our experience of eight years concerning the harmlessness of the BCG vaccine is as follows:

1: It proved to be harmless when administered to monkeys, guinea pigs and rabbits. Of the 400 to 500 animals injected with large amounts of living organisms, only one developed a moderate tuberculosis, and in this case the possibility of an accidental laboratory infection was not entirely excluded.
2: It did not result in the development of clinical tuberculosis in any or possibly may have in only one of the 175 young infants who were not exposed to a known tuberculous source during an observation period which in some instances extended through eight years.
3: Of 515 children vaccinated with living BCG organisms and exposed to a human tuberculous source, only five died of tuberculosis; from their organs, the human and not the bovine type of tubercle bacilli was recovered.
4: In 27 cases the virulence of the BCG strains recovered from cold abscesses caused by vaccination could not be shown to have been enhanced by living in the human body for periods of one to ten months.

There is very little reason to think that the BCG bacilli become virulent at a later time in the vaccinated children, because the incidence of bovine tuberculosis rapidly decreases in older subjects according to the studies of Griffith, Moeller, Park, Gundel and others. To find bovine

tubercle bacilli in adult patients suffering from phthisis is a rarity. Up to date there are but very few such cases published. When one considers that the milk of this and other countries contained living bovine tubercle bacilli in from 15 to 30 per cent of the samples examined, before pasteurization became widely used, and still bovine tubercle bacilli were found only very rarely in older subjects than 15 years of age, it is obvious that the presence of a continually decreasing number of BCG bacilli in the bodies of our children means a correspondingly diminishing danger as the children become older.

TABLE 1

Status of BCG study on May 1, 1935

	1	2	3	4
	TOTAL NUMBER OF CASES	TUBERCULOSIS DEATHS	NON-TUBERCULOSIS DEATHS	PER CENT OF CASES AUTOPSIED
Orally vaccinated BCG children	269	3 (1.1%)	26 (9.7%)	44
Parenterally vaccinated BCG children	421	3 (0.7%)	12 (2.8%)	80
Controls known since birth	345	9 (2.6%)	20 (5.7%)	52
Controls not known from birth with negative initial Mantoux tests	410	11 (2.7%)	17 (4.1%)	36
Total	1445	26 (1.8%)	75 (5.2%)	49

CHAPTER II. IS THE BCG CULTURE EFFECTIVE IN PREVENTING TUBERCULOSIS AMONG VACCINATED CHILDREN?

The answer to this question can be obtained by studying clinically the BCG-vaccinated infants and comparing them with the unvaccinated controls, or by studying the tuberculosis death-rate of comparable cases. The study of tuberculin tests, chest roentgenograms and gains of weight will be the topic of subsequent publications. This paper deals largely with the tuberculosis mortality rates as the gauge of the immunizing effect of the BCG vaccination. However, it is not enough merely to state the difference in mortality rate between the BCG vaccinated cases and the controls; the two groups have to be studied from different points of view in order to see whether they are really comparable.

1. Type of Cases Studied

The first column of table 1 contains the different types of cases included in the BCG study. The "oral BCG babies" are children vac-

cinated by mouth with three 10-mgm. doses of BCG vaccines at intervals of two days within the first ten days of life. Of course, in order to vaccinate them at such an early age, they had to be known to us practically from birth. According to Calmette, oral vaccination should be done during the first ten days of life because at this age the alimentary tract is more permeable to the vaccine than later. Since we entered all oral BCG children in our study at a few days of age, the corresponding control group was also made up of children known from birth. We designated this group as *controls known from birth.* As the tuberculin test of all children at birth is negative, we did not have to tuberculin-test these children before taking them up. This group of controls can be used as a suitable comparison to both the oral BCG children and to those parenterally vaccinated ones who were immunized very shortly after birth; 124, or 29 per cent, of them, were vaccinated within the first month of life. By "parenterally vaccinated BCG cases" we mean children who had negative initial tuberculin tests, no evidence of tuberculosis, and were vaccinated either intracutaneously or subcutaneously with the BCG vaccine. The parenteral method may be used on patients of any age if they are free from tuberculosis. However, because the chance of children developing clinical tuberculosis is different in various environments and at various ages, we tried to obtain all our cases for parenteral vaccination within the first year of life among children of tuberculous families. There were only 124 children among 421, or 29 per cent, who were vaccinated within the first month of life. As the parenteral BCG cases older than one month of age were tuberculin-tested and reacted negatively before receiving vaccination, the cases which we considered the corresponding controls had likewise to have a negative initial tuberculin reaction if over one month of age. Most of these cases, like the majority of the parenterally BCG vaccinated ones, were also not known from birth, but from a later age during their first year. Only 79 of 410 controls, or 19 per cent, had their first Mantoux test after the age of twelve months, and 28, or 7 per cent, of the parenterally vaccinated infants received the BCG later than during the first year of life.

2. Number of Different Types of Cases Studied

Column 1 in table 1 shows us how many different types of cases we studied. We have about 300 to 400 cases in each group. The total number of cases studied is 1,445.

3. Tuberculosis Death-Rate

Column 2 in table 1 is the most important part of the table. It shows the tuberculosis death-rates among the different types of cases. Of course, only similar groups should be compared with one another. The tuberculosis death-rate among the "controls known from birth" is more than twice as high as among the orally vaccinated babies. On the other hand, the negative Mantoux control cases showed a tuberculosis death-rate about four times as high as that among the corresponding treated group, that is, among the parenterally vaccinated BCG babies. The diagnosis of the cause of death can be considered very accurate as all but 5 of 101 children who died of tuberculous and nontuberculous diseases died in hospitals, 49 per cent of them were autopsied, and 50 per cent of the autopsied ones were bacteriologically studied by the Bureau of Laboratories.

4. Nontuberculous Deaths

Column 4 shows the deaths which were due to causes other than tuberculosis. There was a 5.2 per cent nontuberculous mortality in our total group. These deaths were distributed so that the oral BCG children showed the highest, that is, 9.7 per cent, and the parenterally vaccinated children the lowest, that is, 2.8 per cent, nontuberculous death-rate. The explanation of the high nontuberculous death-rate of the orally vaccinated BCG babies is probably caused by the following procedure: At the beginning of our work we made an effort, according to Calmette's suggestion, to keep our babies away from the tuberculous contact for one month or longer after vaccination. As we had no other place to put the children for the purpose of separation, we left them in different hospitals. However, so many of them developed intercurrent diseases and died of hospital infections other than tuberculosis, that we had to discontinue this practice. At present, we do not separate our cases from the tuberculous focus after vaccination if this necessitates hospitalization. We do not think that the BCG itself had any part in the high nontuberculous death-rate, because in the parenterally vaccinated BCG group, the nontuberculous death-rate is lower than in the corresponding control group. If the BCG vaccination were a factor in producing a high nontuberculous death-rate, one would expect a high nontuberculous mortality not only in the oral but also in parenteral BCG group.

5. *Entry Age Difference between Vaccinated and Nonvaccinated Cases*

In order to evaluate the tuberculosis death-rate difference among the BCG and control cases several factors have to be considered. One of these is the age of the child when it was entered in our study.

TABLE 2

Age of cases when they entered the BCG study

TYPE OF CASE	TOTAL NUMBER OF CASES	ENTRY AGES IN MONTHS										
		0–1	1–2	2–3	3–6	6–9	9–12	12–15	15–18	18–21	21–24	Later than 24
Parenterally vaccinated BCG cases	421	124 29%	54 13%	57 14%	67 16%	48 11%	43 10%	5 1%	3 1%	4 1%	2 0.5%	14 3%
Controls not known since birth with negative initial Mantoux tests	410	2 0.5%	40 10%	38 9%	98 24%	76 18%	77 19%	17 4%	14 3%	10 2%	8 2%	30 8%

Table 2 shows clearly that considerably more young children entered the parenterally vaccinated group than were admitted in the control group. Therefore, the parenterally vaccinated infants had more chance to develop tuberculosis than did the controls, assuming that both groups were followed for an equal length of time. Still the tuberculosis death-rate among them is four times less than what it is among the corresponding controls. Table 2 does not contain the orally vaccinated and the control children whom we knew from birth, as there is no entry age difference between them.

6. *The Exposure to Tuberculosis among Our Children*

In order to estimate the comparability of our cases from the point of view of exposure, we tabulated our cases in table 3, columns 1, 2 and 3, according to whether they were not exposed to any known tuberculosis, or whether they were exposed to a case of tuberculosis with positive sputum, or to one having negative sputum. At the beginning of our work, in order to keep the exposure conditions similar, we tried to match our cases with respect to exposure, and made a new case a control or a vaccinated baby according to whether we needed such a case in the treated or untreated group. During the past 24 months, we have alternated the new cases in the order they were reported to us and

when we could obtain consent from the parents have vaccinated every second new case.

In columns 1, 2 and 3 of table 3, we figured out the exposure of all of our cases. We considered a case exposed in the oral BCG and in the "control group known from birth," if exposure occurred at any time during our observation of the case. If both open and closed tuberculosis exposure occurred, the case was listed in the group exposed to open tuberculosis. With the tabulation of the rest of the cases, we had to use a different method. As, irrespective of exposure, a case having a negative tuberculin test was considered free from tuberculosis, and therefore eligible for parenteral vaccination, we did not think it fair to

TABLE 3

Exposure to tuberculosis

	1	2	3	4	5
	EXPOSED TO POSITIVE SPUTUM	EXPOSED TO NEGATIVE SPUTUM	NO KNOWN EXPOSURE TO TUBERCULOSIS	FOLLOWED DURING FIRST YEAR OF LIFE	EXPOSED TO POSITIVE SPUTUM DURING FIRST YEAR OF LIFE
	per cent	*per cent*	*per cent*	*per cent*	*per cent*
Orally vaccinated BCG cases	34	35	31	100	21
Parenterally vaccinated BCG cases	43	34	23	94	35
Controls known since birth	35	44	21	100	34
Controls not known from birth; negative initial Mantoux test	52	32	16	83	43

give consideration to prevaccination exposure unless it occurred within three months prior to vaccination, a period during which the child could have been in the incubation time of tuberculosis. Since we chose this procedure for the parenterally vaccinated babies, and we considered the exposure only from three months prior to the vaccination, we had to use a similar method for the "controls with negative initial Mantoux." Here the exposure was considered from three months prior to the first tuberculin test. Columns 1, 2 and 3 in table 3 show that the exposure of corresponding groups is remarkably similar; however, only one-third to one-half of all cases were exposed to open tuberculosis; about one-third to closed tuberculosis; and less than one-third of the cases were not known to be exposed at all to tuberculosis. As a whole, we feel that the

exposure to tuberculosis is very similar in the groups compared; therefore, the tuberculosis death-rate difference is a reliable one and not the result of unequal exposure.

7. *Exposure to Tuberculosis within the First Year of Life*

As our treated and control cases were found to be comparable when we studied the exposure through the whole of our observation time, we wished to see whether this similarity is true even for the first year of life during which children are known to be more susceptible to fatal tuberculosis than they are later. Also our own experience bears out the fact that the first year's exposure is very dangerous, because 25 of the total of 26 cases who died of tuberculosis were exposed to positive sputum during their first year of life. Columns 4 and 5 in table 3 deal with the exposure to tuberculosis during the first year of life. In column 4 we can see the percentage of our cases which were under observation during the important first year of life. The orally BCG vaccinated cases, and the "controls known from birth" of course were all with us from the time of their birth onward. Ninety-four per cent of the parenterally vaccinated babies were followed during all or part of the first year, whereas only 83 per cent of the controls with negative initial Mantoux tests were with us part of the first year. Column 5 shows how large a percentage of those children who were under our observation during their first year were exposed to open tuberculosis within twelve months of age. In infants who were not seen shortly after birth, the exposure was counted not only from the actual onset of the observation time but from three months prior to this date, because in rare cases an exposure to tuberculosis might not produce objective symptoms until three months have elapsed. For instance, a negative tuberculin test might mean either that the patient was never infected with tuberculosis or that the infection took place more recently than three months. Therefore, every case exposed to tuberculosis shortly before entering our research group was watched from the development of signs of tuberculosis and placed in the "exposed to tuberculosis" group. According to the above described system of tabulation we can see that within the first year of their life, 7–13 per cent less of BCG children were exposed to open tuberculosis than controls. This of course means that the controls as a whole were subject to a somewhat greater risk to develop tuberculosis than were the BCG vaccinated babies.

TABLE 4

	FIRST YEAR						SECOND YEAR						THIRD YEAR					
	Exposed to positive sputum		Exposed to negative sputum		No known exposure to tuberculosis		Exposed to positive sputum		Exposed to negative sputum		No known exposure to tuberculosis		Exposed to positive sputum		Exposed to negative sputum		No known exposure to tuberculosis	
	Total years	Percentage of tuberculosis deaths	Total years	Percentage of tuberculosis deaths	Total years	Percentage of tuberculosis deaths	Total years	Percentage of tuberculosis deaths	Total years	Percentage of tuberculosis deaths	Total years	Percentage of tuberculosis deaths	Total years	Percentage of tuberculosis deaths	Total years	Percentage of tuberculosis deaths	Total years	Percentage of tuberculosis deaths
Orally vaccinated BCG cases	62	1.6	86	0	82	1.2*	60	0	78	0	62	0	59	1.7	69	0	56	0
Parenterally vaccinated BCG cases	89	2.2	80	0	73	0	111	0.9	63	0	71	0	78	0	30	0	43	0
Controls known since birth	98	6.1	139	0.7	71	0	84	2.4	107	0	51	0	64	0	81	0	34	0
Controls not known from birth with negative initial Mantoux test	69	8.7	52	0	45	0	118	2.5	75	1.3	70	0	93	1.1	51	0	66	0

* This is baby M. N. described as a possible congenital tuberculosis case.

8. Yearly Tuberculosis Death-Rate According to Exposure

In the previous tables we handled all our material in one group irrespective of their age. In table 4 we rearranged the whole material according to exposure to tuberculosis and according to age of the children per years. As no deaths due to tuberculosis occurred beyond three years of age we are giving the death rates only for the first three years of life.

In table 4 we totalled under each year the number of years of child life but not the number of children observed in the year. Thus, if during the first year a child was observed for five months only and another for seven months, these two periods are combined and counted as one child year and not as two children. This procedure was suggested to us by Louis I. Dublin, the Statistician of the Metropolitan Life Insurance Company. The exposure in table 4 was considered from birth onward in the orally vaccinated BCG and in the "control group known from birth." In the parenterally vaccinated BCG and in the "control group not known from birth," however, exposure was counted only from the date of vaccination and from the time of the first Mantoux test, respectively. In all the groups a child once exposed was left in the category of the exposed children. If exposure to positive and to negative sputum occurred in the same case, the positive-sputum exposure determined the group in which the case was placed.

From table 4 it is obvious that the protective value of the BCG vaccination is most advantageously used when it is tried on cases exposed to positive sputum. In this group of children during the first year of life, the orally and parenterally vaccinated children showed four times less tuberculosis deaths than corresponding control cases. In later years and with exposure to negative sputum the tuberculosis death-rate difference between BCG vaccinated and control children is less marked.

9. The Statistical Reliability of the Death-Rates from Tuberculosis

As no one in the BCG group is especially trained in statistics, it seemed desirable that our results should be analyzed by someone expert in statistics and, at the same time, specializing in research on tuberculosis. Such a person we found in Dr. Emil Bogen who, at Olive View Sanatorium, has done the best and most extensive animal experimentation with BCG and heat-killed tubercle-bacillus vaccines. Dr. Bogen was kind to spend about two months with us in going over our material

in detail, and has been kind also in allowing us to quote in the present paper a portion of his statistical analysis of our results.

The probable error of a relative frequency is most readily determined as the square root of the product of the positive and negative frequencies, divided by the square root of the number of cases, and multiplied by the factor 0.6745, i.e., $0.6745 \sqrt{\frac{p.q.}{N}}$

This formula is not accurate when applied to very small numbers, or when the proportion of cases in one group is less than two or three per cent, but may be taken as a lower limit of such error.

The probable error of a difference in percentages is equal to the square root of the sums of the squares of the probable errors of the two percentages themselves, i.e., P.E. of A + B = $\sqrt{\text{P.E. of A}^2 + \text{P.E. of B}^2}$

No difference in frequencies can be considered of statistical significance if it is less than several times its own probable error.

Applying the above three simple rules, we find that in table 1 the probable errors of the percentages in column 2 are 0.42, 0.28, 0.57 and 0.53, respectively. The differences in the percentages between orally vaccinated children and the controls known since birth are then $2.6\% - 1.1\% \pm \sqrt{0.42^2 + 0.57^2} = 1.5 \pm 0.7$ which is only 2.1 times its own probable error and therefore not statistically significant. In other words, although the orally vaccinated babies showed a lower mortality rate than corresponding controls this might happen by chance in similar groups about once in every three times. The differences between the parenterally vaccinated vs. controls with initial negative Mantoux tests is $2.7\% - 0.7\% \pm \sqrt{0.28^2 \div 0.53^2} = 2.0 \pm 0.6$ which is 3.3 times its own probable error, and thus could not be expected to occur by chance more than one time in thirty-seven.

Combining, we find that the difference in the mortality rate between the groups of vaccinated infants and the two groups of controls would be

Vaccinated 690 cases, 6 deaths $0.9\% \pm 0.24$
Controls 755 cases, 20 deaths $2.7\% \pm 0.40$

Difference $1.8\% \pm 0.47$ or 3.9 times the probable error, which would occur by chance in less than one per cent of the times, and is therefore of probable statistical significance.

The fact that the entire group of vaccinated infants show a mortality rate that is lower than that of the entire group of controls by more than three times its probable error indicates that there has been a real difference in the tuberculosis mortality rates between these two groups. Whether this difference has been due to the vaccination, or to other factors in the choice of

cases and controls, exposure, etc., had to be studied by closer examination of the actual data and records, as has been shown in the previous tables.

As has been stated, owing to the small percentages here involved, the probable errors obtained are somewhat smaller than the true errors which might be determined by somewhat more complicated calculation. Another simple means of calculating the errors is by means of Pearson's Chi square formula for goodness of fit, placing the data in the form of a contingency table. When this is done we find Chi square here equal to 6.46 which would correspond to a value of 3.8 times the probable error of the difference, which is quite close to the figure obtained by the previous method.

Applying similar methods to the total number of children exposed to positive sputum, we got

Vaccinated 459 years, 5 deaths 0.9%
Controls 525 years, 17 deaths 3.2%

and a Chi square value of 5.15 or a value of 3.4 times the probable error of the difference.

The differences here observed, of between three and four times the probable error of the difference, are probably significant though by no means conclusive; the differences observed probably are real and not merely the results of random sampling. Personal investigation of the manner in which this work has been done reveals no apparent cause for the differences, other than the vaccination, and it appears, accordingly, that the results so far support the claims that vaccination with BCG is of real protective value against deaths from tuberculosis in infancy. It is hoped that the work may be continued, so that this indication may be more securely established, but the experiment so far seems to justify the application of this form of immunization in other groups of infants who are particularly apt to be exposed to the danger of tuberculous infection.

10. Cases Still under Observation

As the BCG staff is a limited one, we had to choose between following-up a small number of cases indefinitely or a larger group for a limited length of time. We regret not being able to continue studying these children who were followed so carefully from so many points of view during their infancy and early childhood, at least beyond their puberty. Such a long and careful follow-up of children of tuberculous families would be unique, rare and valuable. However, as we had to make a compromise, we felt that from the point of view of the BCG investigation, it is more important to watch enough babies in the first five years

of their lives than to observe fewer of them for a longer period. We think so because the tuberculosis death-rate is considerably higher in the first five years of life than in the second five-year period. As a matter of fact, the tuberculosis mortality rate is highest during the first

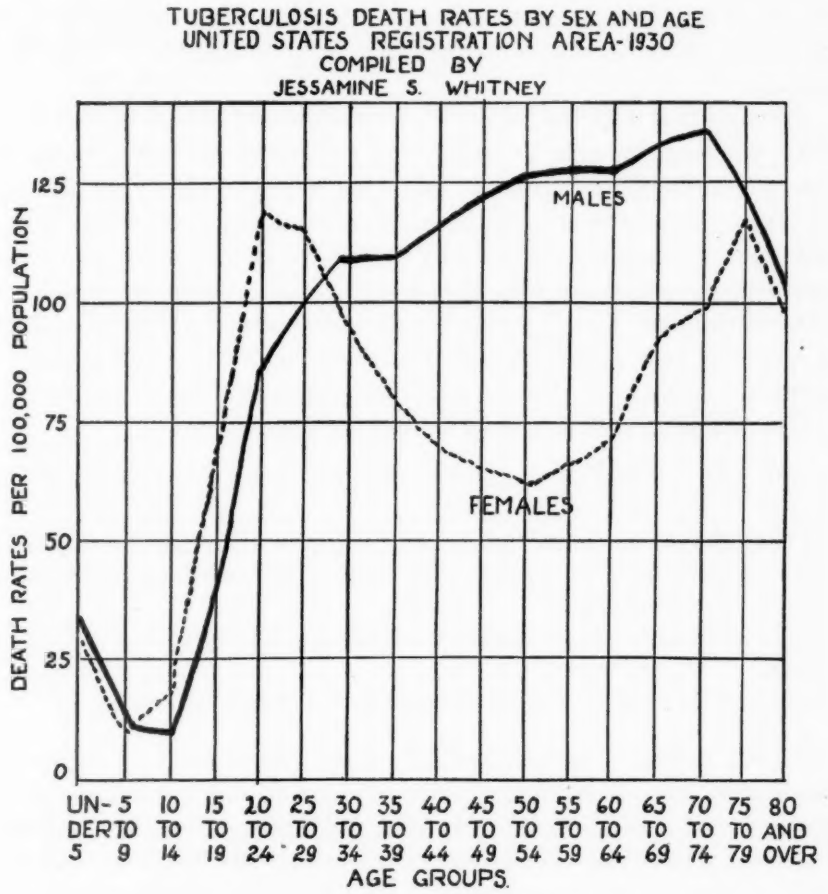

CHART 1

year of life and gradually declines to the lowest point at five years. From five to ten years, it becomes stationary for males at the low level which it reached at five years, and for females it rises a trifle. Onward from the age of ten, the tuberculosis death-rate rises sharply in both sexes and between 20 and 25 years of age, it reaches the maximum

for females and between the ages of 70 and 75 reaches the maximum for males. This description is well illustrated on chart 1.

Looking at chart 1, one feels very strongly that the BCG study should continue until the child reaches maturity, and should not stop at the fifth year of life. However, while the study has up to 1935 been supported chiefly from private funds and much less from city budgets, we could not carry on a work increasing in size throughout a whole generation.

We hope that with the help of the Department of Health of New York City we may be able to reopen the records of the cases which we discontinued and still be able to follow the others which we are planning to take up in the future. In the course of our eight years' study we discontinued 71 per cent of our orally vaccinated cases, 18 per cent of our parenterally immunized ones, 39 per cent of our controls whom we knew from birth onward, and 50 per cent of those controls which had a negative initial tuberculin test. In the selection of the cases which we stopped following we tried to use a logical system.

The following were the bases for discontinuation:

1: All children except 50[3] nonexposed oral BCG babies on reaching five years of age.
2: The tuberculous member died, and there never was any contact; or, if there had been some contact, this had ceased a year or more previous to the time of discontinuation.
3: The children live in the outskirts of New York City, and are difficult to follow.
4: The family became incoöperative and chose not to be followed.

In our statistics, we give credit to discontinued cases up to the age when they were discontinued. We also are planning a survey of our discontinued cases by looking up each of them in the list of the tuberculosis deaths of the City of New York to find out, if we can, whether any of them died of tuberculosis in the City after the time we stopped following them. The reasons that the greatest number of cases, that is, 82 per cent are still followed among the parenterally vaccinated BCG babies is that we started this method of vaccination two years later than we did the oral vaccination and 2½ years later than the collecting of controls; so the parenterally BCG-vaccinated cases are still for the

[3] The purpose of continuing these 50 children is to have additional evidence of the harmlessness of the Calmette vaccine.

most part less than five years of age. Some of the controls known from birth are also very young, but a great many of them have finished their fifth year. This explains why only 50 per cent of them are still followed.

CHAPTER III. SHOULD THE BCG VACCINATION BE USED AS A PUBLIC HEALTH MEASURE?

One might object to the public-health use of the BCG vaccine because, as has been shown in table 1, the tuberculosis death-rate among our controls, that is, without the use of the BCG vaccine, is only 2.7 per

TABLE 5

Tuberculosis death-rate of the general population of New York City as compared with tuberculosis death-rate of children of tuberculous families

	FIRST YEAR		SECOND YEAR		THIRD YEAR	
	Tuberculosis death-rate	Ratio of tuberculosis death-rates	Tuberculosis death-rate	Ratio of tuberculosis death-rates	Tuberlosis death-rate	Ratio of tuberculosis death-rates
	per cent		*per cent*		*per cent*	
Tuberculosis death-rate of children of tuberculous families in New York City. (Our control cases.)	2.7	45:1	1.2	24:1	0.3	7:1
Tuberculosis death-rate of children of *open* tuberculous families in New York City. (Our control cases.)	7.2	120:1	2.4	48:1	0.6	15:1
Tuberculosis death-rate of general population of New York City, compiled by Dr. John Walsh and Mr. G. J. Drolet for 1930, 1931, 1932	0.06		0.05		0.04	

cent. On the surface, this figure seems to be so low that to some it might not warrant public health considerations.

Looking at table 5, one can see that the comparison of the tuberculosis death-rate of children of tuberculous families with the tuberculosis death-rate of children of the general population of New York City within similar ages shows striking differences. The same 2.7 per cent death rate among our control cases is 45 times greater than the corresponding figure among children of the general population. The ratio among deaths in open tuberculous families for the same age-groups becomes 120 times more than the corresponding number of the general population. These differences are so enormous that one necessarily feels that it is worth while to make every effort to diminish the risk of death due to

tuberculosis among children of tuberculous families. As the children grow older, the contrast between the death-rates of the groups compared becomes smaller. This fact verifies our effort to give the BCG vaccine as early as possible.

Of course we realize that even with the use of BCG vaccine parenterally we are able to cut the death-rate only to its fourth. However, we think that, if we found the way to reach all children of tuberculous families at birth and we had means to separate them from tuberculous contact, as Wallgren did, three months before and as long after vaccination until allergy to tuberculin appears, the BCG could be made very much more effective.

As the BCG vaccination of children has been carried on only for 14 years in Europe, and eight years in this country, and there are as yet very few well-controlled human experiments with it reported in the medical literature, the vaccination should be continued in several well-equipped centres on a research basis as well as routinely. Our material in New York City is especially valuable because it is well controlled, is carefully analyzed, and has already been assembled throughout eight years. The same material lends itself not only to the evaluation of the BCG vaccination, but also to the study of many other factors influencing the prevention, development and cure of tuberculosis.

CONCLUSIONS

1. The evidence obtained by other workers and by us shows more and more clearly that the BCG vaccine is harmless to animals and to human beings.

2. In our experience the parenteral administration of the Calmette culture is more effective than the oral, because the tuberculosis death-rate decreased to its half when the oral method was used, and to its fourth when the BCG vaccine was injected intracutaneously or subcutaneously.

3. As the use of the BCG vaccine is harmless and increased considerably the resistance to tuberculosis, its use should be urged as a public-health measure for the prevention of tuberculosis in those who have not yet become infected and who may later be exposed to tuberculosis in their own families.

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A STUDY OF THE PATHOLOGY OF EXPERIMENTAL PULMONARY TUBERCULOSIS IN THE RABBIT[1,2]

E. M. MEDLAR AND K. T. SASANO

A main problem of tuberculous infection in man that has eluded solution to date is the rationale of localizing, cavitating pulmonary disease. Primary tuberculous infection through ingestion of contaminated food has in large part been controlled by the establishment of a safe milk supply and the marked advances in the eradication of bovine tuberculosis. The control of pulmonary tuberculous infection is much more difficult because this form is brought about in large part by the contamination of the air with material from open pulmonary disease. As long as air contamination with tubercle bacilli exists, tuberculous infection of the lung will persist. It would seem, then, that the solution of this basic problem of aerogenous contamination depends in large measure upon the thorough understanding of the pathology of pulmonary tuberculosis and the application of this knowledge to the control of the disease.

Many clinical and pathological classifications of pulmonary tuberculosis have been devised. All of them have been attempts to clarify the problems presented by the complex clinical and pathological manifestations of the disease. The diversity of opinion expressed in these attempts to elucidate the facts of importance in pulmonary tuberculosis indicates clearly that the plain facts of the underlying causes of the chronic, progressive, cavitating disease are but partially known.

The authors are aware of the extreme difficulties that confront those who attempt to clarify the problem through the study of human material alone. They also recognize that fallacies may enter into any attempt to carry observations made upon experimental animals over to the human problem. There are, however, phases of the disease that can be obtained only from carefully controlled animal experimentation. We are

[1] From the Hegeman Research Laboratory of the Metropolitan Life Insurance Company, Mount McGregor, New York.

[2] Presented as part of a Joint Symposium on the topic, *Present Concepts of Tuberculous Infection and Disease: Their Principles and Application*, at the thirty-first annual meeting of the National Tuberculosis Association, Saranac Lake, New York, June 27, 1935.

well aware of the fact that no one may make with assurance comparisons of or draw analogies between the pathology of pulmonary tuberculosis in man and in animals until the various types of lesion found in the human lung have been duplicated in the experimental animal. In so far as the pulmonary lesions in man are concerned, the important pathological processes are localization, progression, cavitation, bronchogenic spreads and retrogression. These phases of the disease must be obtained in experimental animals before such experimentation can materially aid in the solution of the problems presented by the human disease.

In an infectious disease the seed, the soil and the lapse of time after the seed and soil are brought together are the three factors of greatest importance. These factors apply with equal force whether the disease is naturally contracted or is experimentally produced. A valid deduction cannot be obtained in the study of an infectious disease, however produced, without a very careful consideration of the interplay of these prime factors. In the study of the problem of human pulmonary tuberculosis it must be fully recognized that all of these factors are entirely beyond control; so that those who attempt to draw deductions relative to the pathological processes observed must realize that, whatever their inferences may be, they are drawn from uncontrolled material.

In the field of animal experimentation conditions can be at least partially regulated. The natural "set-up" of the host, relative to inherent susceptibility or resistance to an infection, is largely unpredictable. The soil may be tampered with in various ways and made more susceptible or more resistant, but otherwise it is ungovernable. Certain properties of the seed may be roughly evaluated. The virulence or pathogenicity of the specific microörganism can be fairly accurately determined through numerous animal tests. The preservation of degrees of virulence remains, at present, largely in the lap of the Gods, for the factors which influence this condition are but little understood. The dosage (quantity of seed) used and the way in which the seed is implanted in the soil is a matter of choice. The time-factor can always be determined. Thus, in carefully conducted animal experimentation one has an opportunity to study the interplay of the factors which determine the eventual outcome of the struggle between the seed and the soil. If, under such conditions, pathological lesions similar to those observed in uncontrolled human disease can be obtained then one should be able to understand more clearly its human pathology.

From the vast amount of investigation of the problem of tuberculous infection in man there has accumulated very definite evidence that this disease differs in the child and the adult (1) and that different races (2), (3), (4) do not react to the infection in the same way. In other words, the soil in the human race varies in some way so that the pathological manifestations and the eventual outcome of the disease depend to some degree upon the race and age of the individual infected. In so far as the white race is concerned, there is a considerable conviction that there is a childhood type and an adult type of disease (1). The childhood type is regarded as the pathological reaction to a first infection and the adult type to a reinfection (or, more accurately perhaps, *reinfections*). That is, the first infection alters the soil in some way so that any subsequent infection brings about a different type of tissue reaction. To some observers this change in character of the pathological reaction can best be explained by the fact that the first infection has induced a sensitized or allergic state of the tissues. The apparent differences in the first and reinfection types has led to the placing of great stress upon the primary complex of Ghon (5) and the primary, secondary and tertiary stages of the disease, as propounded by Ranke (6).

In the adult or reinfection type of disease it is generally recognized that localization occurs predominantly in the upper portion of the pulmonary field, apical or subapical. The phenomenon is so common that correct diagnoses of pulmonary tuberculosis are often made from roentgenogram shadows in this region without any other corroborative evidence. The reason for this localization of the adult disease is but little understood. The influence of an allergic state and the possibility of anatomical peculiarities of the lung structure have both been suggested as plausible explanations.

METHODS OF PROCEDURE AND RESULTS OBTAINED

In animal experimentation it is possible to investigate thoroughly the concepts given above. It is the purpose of this report to give in brief the results obtained in rabbit experiments devised to study the phenomena of primary infection, reinfection and the localization of tuberculous foci in the parenchyma of the lung. In these experiments cultures of tubercle bacilli of different degrees of virulence have been used. Various amounts of the bacillary growth have been inoculated. The effect of vaccination with both living bacilli of low virulence and with heat-killed bacilli of high virulence has been investigated relative to

the type of pathological process present when reinfection is produced through the introduction of living bacilli of high virulence. Throughout these studies the intravenous route of inoculation has always been used. This has been done purposely so that all portions of the pulmonary tissue would have the same opportunity of having tuberculous lesions develop and of becoming sensitized. It is recognized that this is not the way natural infections occur. However, in natural infections it is quite unlikely that an equal and simultaneous distribution of tubercle bacilli to all parts of the pulmonary parenchyma occurs.

The cultures used in the study are three strains obtained from a single original culture. These strains represent three grades of virulence. We have obtained them during our studies of Calmette's culture (*BCG*). The original culture of *BCG*, which has been under study in this laboratory since 1926, has always remained at a low level of pathogenicity when continually grown on a bile-glycerin-potato medium. After many attempts we succeeded on one occasion in obtaining a very virulent strain as a result of change of environment in culture medium. This virulent organism has been maintained on enriched media and has largely retained its high potency. We have used this as the bacillus of high virulence in the studies to be reported. To determine whether the culture might lose its virulence it has been transferred back to the bile-glycerin-potato medium. Considerable difficulty was encountered in obtaining growth on this medium at first, but for the past two years it has been grown constantly on such a medium. As a result, it has lost a considerable amount of virulence, but it is still of higher potency than the original *BCG*. In our studies we have employed this as the organism of medium virulence. We have, then, three variants of a single strain of tubercle bacillus exhibiting different characteristics with which we have become familiar over a period of eight years of study.

In plates 1 to 6 we show the variety of pathological lesions obtained as a result of our animal experimentation. The illustrations have been carefully selected to demonstrate the phenomena of localization, progression, cavitation, bronchogenic spread and retrogression, the points of prime consideration in pulmonary tuberculosis in man.

No attempt has been made to obtain a statistical analysis of the results of the various experiments. We were primarily interested in finding out whether a variety of lesions could be obtained similar to those known to occur in the human tuberculous lung. Although several hundred rabbits have been used, the number in single experiments have

never exceeded twenty. With such small groups statistical analyses would obviously be unreliable.

Some of the marked contrasts of the results obtained in the experiments are as follows: Inoculations of from 10 to 50 mgm. of living bacilli of low virulence always caused marked pulmonary disease which very rarely killed. Those animals which died did so at the height of the pulmonary involvement (4 to 6 weeks), and we are of the opinion that these deaths were due primarily to the marked interference with pulmonary function rather than to toxicity of the infection. No animal has died that survived two months, and many have been kept alive for three years. In the large majority of instances the pathological process has completely resolved within a year. In a few animals pathological lesions have persisted for three years after inoculation. In such cases there was no evidence of cavitation or of bronchogenic spreads. Reso-

PLATE 1

Explanation of Photomicrographs

All photomicrographs are magnified about twice.

Figures 1 to 3 from a group of rabbits inoculated intravenously with 20 mgm. of tubercle bacilli of low virulence. Show uniform progression and retrogression of lesions.

Fig. 1: 2 weeks.

Fig. 2: 1 month.

Fig. 3: 11 months. This animal showed as much disease by roentgenogram at 1 month as did that of fig. 2.

lution has occurred more rapidly in the anterior and ventral portions of the lung than in the posterior and dorsal portions.

Inoculation of living bacilli of high virulence always caused death. When 1 mgm. of culture was used death always occurred within two months. With the use of 0.01 mgm. of culture death always ensued within six months. The tuberculous lesions progressed evenly in all parts of the pulmonary tissue: That is, it seemed that wherever the virulent bacilli lodged in the pulmonary tissue progressive spreading lesions ensued. The amount of involvement of the pulmonary parenchyma depended in large part upon how long the animal lived after being infected. Due to suppurating and ulcerating lesions, bronchogenic spreading of the disease was very common. Gross cavitation was never observed.

Animals inoculated with cultures of medium virulence have all eventually succumbed to the infection. When 1 mgm. was inoculated some

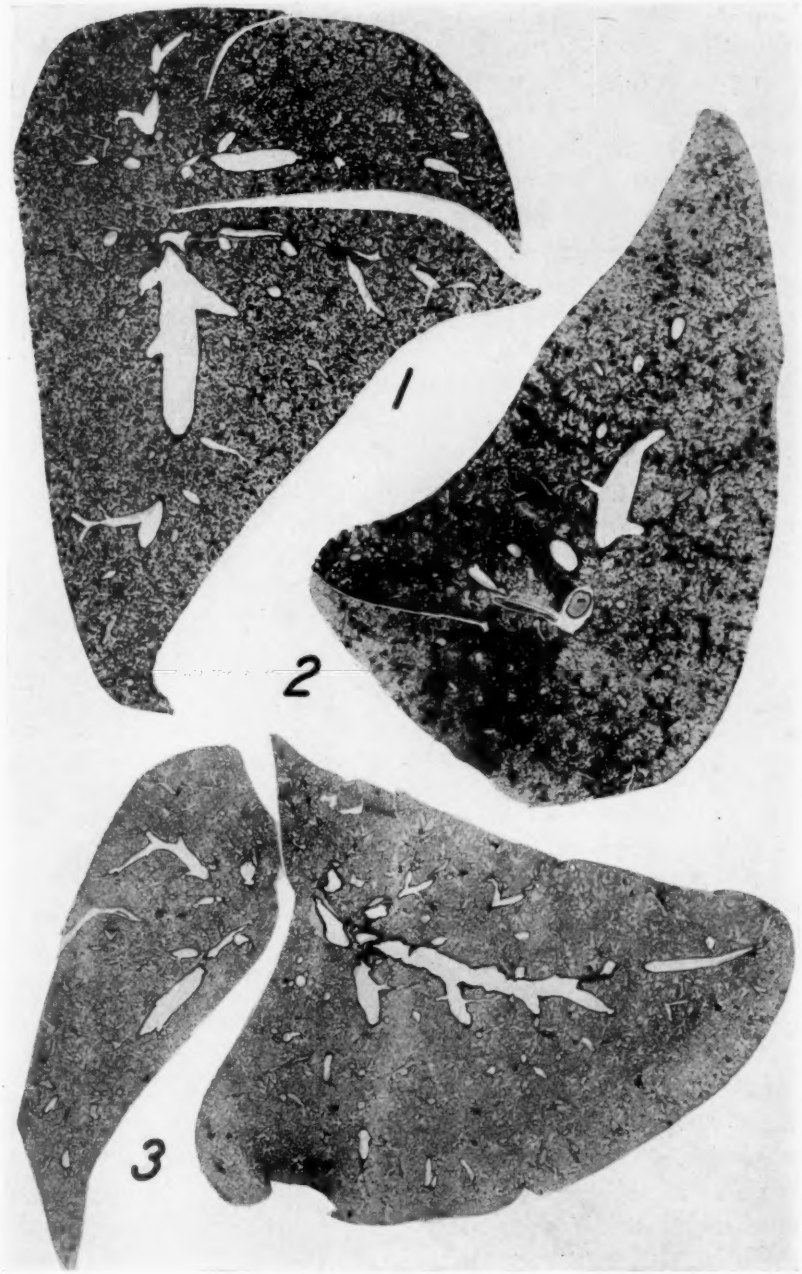

PLATE 1

of the animals lived for over 6 months. When 0.01 mgm. was injected some of the animals have survived for 2 years. Animals which died within two months always showed a uniform development of the pathological changes throughout the lung. Animals surviving for six months presented varying degrees of involvement. On occasion, there was a marked general infection. Some of the animals showed a complete resolution of the pulmonary lesions in the anterior and ventral portions of the lung parenchyma with gross cavitation and bronchogenic spreading in the posterior and dorsal areas. In some instances bronchogenic spreads also occurred in the anterior and ventral lung parenchyma. Animals given a small infecting dosage (0.01 mgm.) and living for over one year always showed complete resolution of the primary tuberculous

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PLATES 2 AND 3

Figures 4 to 8 from groups of rabbits inoculated intravenously with tubercle bacilli of high virulence. Disease shows uniform progression without retrogression. Nos. 4 to 6 were given 1 mgm. each, and 7 and 8 0.01 mgm. each.

Fig. 4: 2 weeks.

Fig. 5: 1 month.

Fig. 6: 2 months.

Fig. 7: 3 months.

Fig. 8: 6 months.

Figures 9 and 10 show a comparison of the disease in vaccinated and nonvaccinated rabbits. Note uniform seeding and development of lesions.

Fig. 9: Nonvaccinated rabbit: 1 mgm. highly virulent bacilli intravenously, killed after 2 weeks.

Fig. 10: Vaccinated rabbit. Reinfected with same dosage of same culture as no. 9. Animal died in 12 days.

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lesions in the anterior and ventral portions of the lung with gross cavitation in the dorsal and posterior parts. Bronchogenic spreads as a result of spilling over from the cavities were occasionally encountered. In some of these animals we considered that death was due to extensive renal tuberculosis rather than to the pulmonary disease.

None of the vaccinated animals died as a result of the vaccination. Disseminated pulmonary foci, which usually completely resolved within six months, were produced. Reinfection with a uniform dosage of 1 mgm. of bacilli of high virulence was given three to six months after vaccination. This lapse of time was allowed so that the vaccination lesions would largely have resolved. In the vaccinated reinfected animals extensive pulmonary involvement was present within two weeks.

PLATE 2

PLATE 3

An occasional animal died in ten days with as much disease present as in a nonvaccinated rabbit at the end of a month. Some lived for over six months. In these latter animals a marked resolution of the tuberculous lesions had occurred in the anterior and ventral lung field with gross cavitation and bronchogenic spreading in the posterior and dorsal areas.

The occurrence of gross cavitation in the posterior and dorsal portions of the lung along with resolution of tuberculous lesions in the anterior and ventral areas in rabbits living over six months on our medium virulent strain and vaccinated reinfected groups led us to an investigation of the possibility of altering the localization of progressive pulmonary lesions by changing the posture of the animals. While this work has been in progress for over two years the inherent difficulties of the problem have greatly hindered its solution. The results obtained to date are of sufficient significance, however, to warrant a preliminary report. Rabbits do not take well to a continuous alteration of their normal posture. After many trials we found that they could withstand being supported in an upright position about ten hours daily if allowed to go back to their normal position for the remainder of the day. The animals were fitted with a metal corset around their chests with a portion extending over and supporting the abdomen. They were then hitched to an overhead trolley in such a position that they were resting comfortably on their haunches. In this position they could move about to a considerable extent but they could not avoid the upright position. The animals were suspended daily at 7 A.M. and placed back in normal position at 6 P.M. Twenty animals have survived over a month after infection under the above regimen, seven have lived over three months, and two have survived for eight months. In all of these animals a single intravenous inoculation of 0.05 mgm. of bacilli of medium virulence was given.

In all of the animals which have lived over three months under the above conditions a spreading tuberculous lesion or lesions was found in the anterior portion of the pulmonary field with resolution of tuberculous lesions in the large midportion and small spreading lesions in the posterior portion. To date no gross cavitation has been observed. We have never seen such localization of tuberculous lesions in rabbits not suspended in the upright position. The lesions in the posterior pulmonary field are considerably smaller than are those found in rabbits inoculated with the same amount of the same culture and kept continu-

PLATE 4

Figs. 11 to 14 show a comparison of disease in vaccinated reinfected and nonvaccinated first-infection rabbits. Note close similarity between 11 and 12, and between 13 and 14.

Fig. 11: Nonvaccinated rabbit, given 1 mgm. of tubercle bacilli of medium virulence intravenously. Died in 6 weeks.

Fig. 13: Rabbit from same group as no. 11. Died in 5 months. Note the contrast in the disease of two specimens. Rabbits 11 and 13 had similar roentgenogram shadows at 1 month after infection.

Fig. 12: Vaccinated rabbit reinfected with 1 mgm. of bacilli of high virulence inoculated intravenously. Died in 1 month.

Fig. 14: Rabbit from same group as no. 12. Died in 6 months. Note contrast between nos. 12 and 14. These two animals showed a comparable amount of disease by roentgenogram at 1 month.

PLATE 4

PLATES 5 AND 6

Figs. 15 to 18. Taken from rabbits given a single intravenous inoculation of 0.02 mgm. of bacilli of medium virulence.

Fig. 15: Killed at 3 months. Note 3 progressing lesions in lower tip of lung with retrogression of lesion in remainder of lung.

Fig. 16: Killed at 18 months. Animal very ill. Note that progressive lesions seen in no. 15 have now gone on to cavitation. This animal had very extensive renal tuberculosis.

Fig. 17: Died in 13 months. Note cavitating lesions in same location as no. 16. Also tuberculous pneumonia due to extensive bronchogenic spreading from cavities at the opposite end of the lung.

Fig. 18: Killed at 18 months. Animal very ill. This animal showed the illustrated cavity at the posterior tip in one lung and no such lesion on the opposite side. No progressive tuberculous lesions in any other portion of the pulmonary tissue. Extensive renal tuberculosis was present.

Figs. 19 to 21. Show the change in location of progressive tuberculous lesions obtained with a change of the posture of rabbits. These animals were given a single intravenous injection of 0.05 mgm. of bacilli of medium virulence.

Fig. 19: Killed at 3 months.

Fig. 20: Died at 5 months.

Fig. 21: Killed at 8 months.

Note that the most extensive lesions are at the anterior extremity of the lung but that there are also smaller progressive tuberculous foci at the posterior extremity.

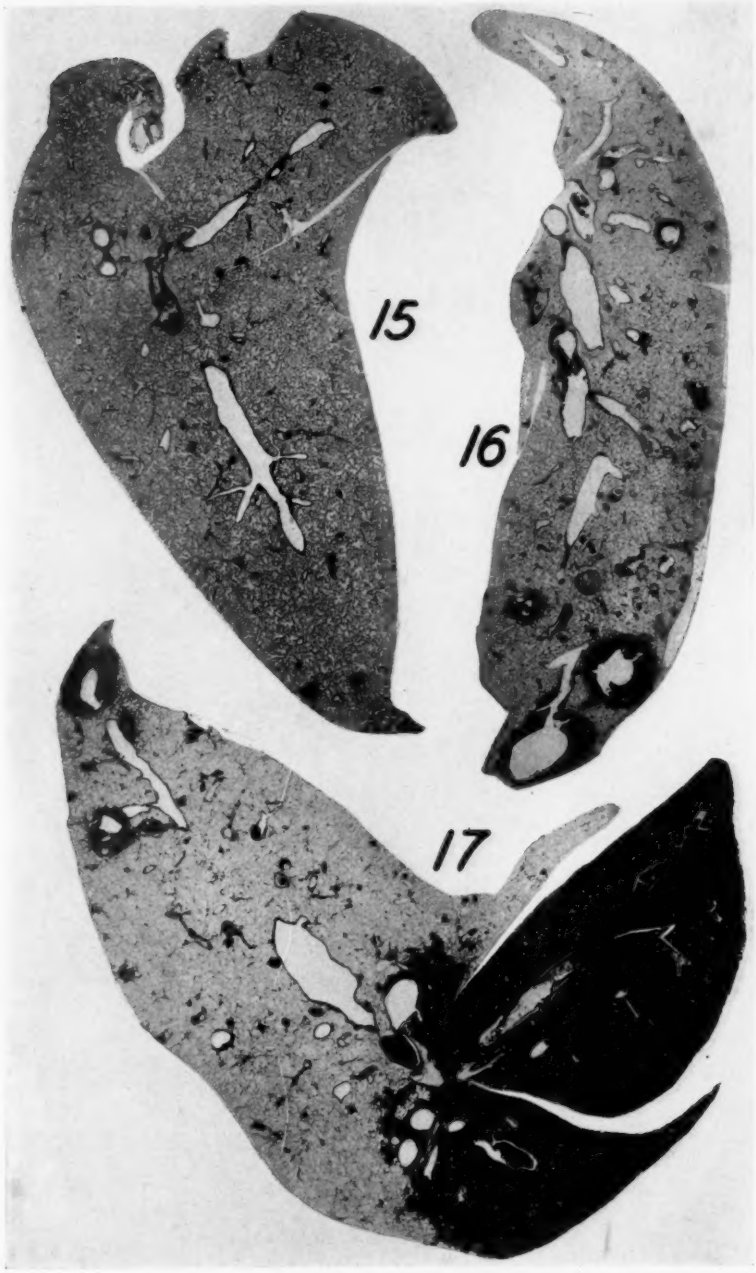

PLATE 5

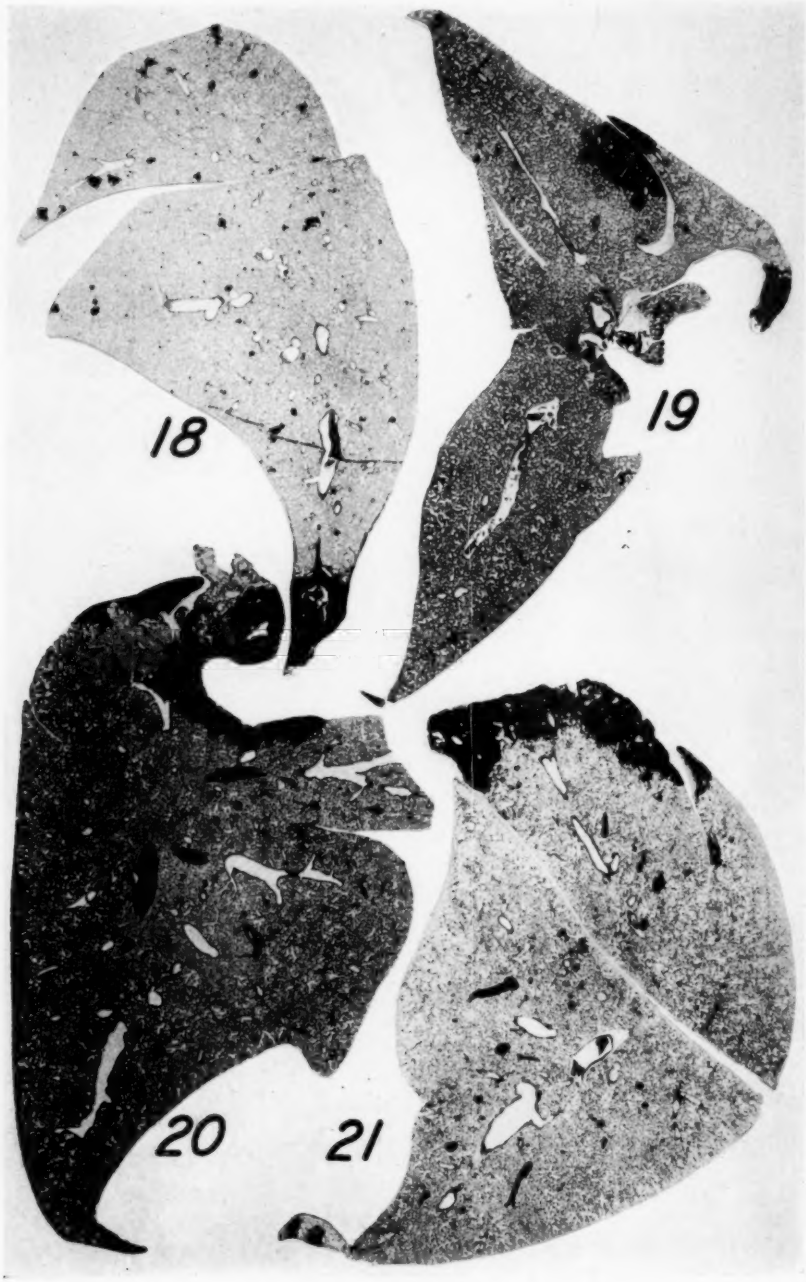

PLATE 6

PLATE 7

Fig. 22: Roentgenogram of rabbit in normal position. When cavitation occurs in rabbits in this position the lesions are almost wholly within the encircled area.

Fig. 23: Roentgenogram of rabbit in suspended position. The main progressing disease now shifts to the area within the circle.

ously in their normal position. This peculiar shift of the main progressing tuberculous process from the caudal to the cephalic portion of the lung parenchyma with the change of posture from normal to upright would appear to have opened up a new avenue of approach toward the explanation of the rationale of apical or subapical tuberculosis in man. In plate 7 the enclosed areas show the position in which the largest spreading lesions are found in the rabbit in the normal and in the upright position.

COMMENT

In this article we have presented the type of lesions obtained in the rabbit which simulate the main pathological features of tuberculous lesions in the human lung. Since these lesions have been obtained under experimental conditions in which many factors have been known and controlled, it would seem that our data make possible a more plausible explanation of the pathology of pulmonary tuberculosis than could possibly be obtained from the study of human lesions wherein all factors are beyond control.

The first point of significance is that by intravenous inoculation whereby all portions of the pulmonary tissue have been evenly seeded with bacilli we have obtained all types of lesions. This would seem to indicate that the inhalation or natural route of infection is not of prime importance in determining the localization of progressing, cavitating tuberculous lesions. In using the intravenous method of inoculation there is the disadvantage of infecting other organs, especially the kidney. However, lesions in organs other than the lung cannot always be avoided in experimental animals even by the use of the inhalation method.

The second point of importance is that the allergic condition of the tissue or the occurrence of a primary infection with a subsequent reinfection are not of as great importance in the localizing of cavitating tuberculous lesions as has been believed. A primary infection alters the soil so that a much more prompt and vigorous response is made when a second infection occurs but the type of cellular pathology differs, not in the type of cells responding, but in the number and proportion of such cells. In our experiments every part of the pulmonary tissue has had an equal opportunity to show an equal development of tuberculous lesions. This has occurred consistently when tubercle bacilli of high virulence have been inoculated. A similar condition has always existed

during the first month or so following injection of bacilli of low or medium pathogenicity and also following the inoculation of virulent bacilli after vaccination. If, however, animals lived for several months after being inoculated with bacilli of medium virulence or after the introduction of bacilli of high virulence following vaccination, a difference was noted in the behavior of the tuberculous lesions in various portions of the lung. In some areas the lesions resolved completely, while in other parts of the same lung they progressed to cavitation. Even in the animals inoculated with bacilli of low pathogenicity the lesions resolved more rapidly in some portions of the lung parenchyma than in others. The differences in behavior of the tuberculous lesions in different areas of the lung in vaccinated rabbits which were later infected with virulent tubercle bacilli throw much doubt upon the rôle that allergy has been supposed to play in the production of cavitating and spreading pulmonary lesions. The fact that localizing, cavitating and spreading lesions (the so-called adult human type) have been obtained from first infections with bacilli of medium virulence creates grave doubt concerning the essential pathological difference between a first and a subsequent infection or between the so-called childhood and adult types of disease.

That the soil is altered as a result of a first infection we believe is indisputable. Our findings reveal however that, at most, the alteration of the soil can be but one factor that may lead to a localizing cavitating tuberculous lesion. We have demonstrated that, in obtaining a proper balance between an unaltered soil and the virulence and dosage of the seed, lesions similar in all essentials to those observed in altered soil can be obtained. In other words, it would seem that the factor of greatest importance in cavitating lesions is the establishment of a certain balance between the host and the parasite. This balance may occur in either a first or a subsequent infection.

The third and perhaps most important fact uncovered in these studies is the site where progressive cavitating lesions develop within the lung. In our experiments an equal opportunity was afforded for the development of such lesions in all portions of the lung parenchyma. That they occurred in only certain areas is of great significance. In the rabbit in normal position the diaphragmatic and dorsal area is the only portion in the lung where we have observed cavitation. Roentgenograms of the rabbit in a normal position show that the place where cavitation was found is the highest portion of the lung. This area, due to posture,

is analogous to the apical and subapical portion of the human lung. When we altered the posture of the rabbit, so that a similar position of the rabbit and human lung was obtained, a change of the localization of the major pathological process to the upper portion of the pulmonary field occurred. To date the failure to obtain gross cavitation is probably due to the fact that the animals have not lived long enough for this phenomenon to develop. We were unable to do away entirely with progressing lesions in the caudal extremity of the lung. The lesions in this region were, however, always less in extent than in the cephalic portion.

The change of site of progressive tuberculosis which occurred when the posture of the rabbit was altered may lead to a truer concept as to why there is a predilection for tuberculous cavities to occur in the upper portions of the human lung. From our experiments it would seem that, due to posture, there is a certain portion of the lung which affords the tubercle bacillus a better chance to survive and cause a chronic progressive disease. That this is not due to any peculiar normal anatomical structure of the lung tissue is suggested by the fact that a change of position leads to a change of location of the progressive lesion. An alteration of the condition within the lung field probably occurs with the change of posture, since emphysema develops in the upper portion of normal rabbit lungs when they are placed in the upright position for ten hours daily for several weeks. There is a possibility of an altered blood and lymph flow, of a difference in gaseous exchange, or of some undefinable chemical set-up in certain pulmonary areas due entirely to posture. These are mere conjectures. Frankly we admit, no conclusive evidence is at hand as to why the progressing, cavitating, tuberculous lesions localize as they do under the conditions of our various experiments.

Aschoff (7) regards progressive pulmonary phthisis in man as an extension of the process from a reinfection of the apex of the upper lobe, the seeding progressing craniocaudally. He believes that only a small portion of those infected develop a progressive pulmonary disease. Thus, referring to the observations of Puhl, he deduces that two-thirds of those having had a primary infection show evidence of a reinfection, and, of those reinfected, at least 50 per cent get entirely well. Aschoff regards the deforming scars found in the upper portion of the human lung as representing a healed reinfection. We are of the opinion that such scars may represent either a primary lesion or reinfection that has

healed. Nevertheless there is definite evidence that a considerable number of tuberculous infections of the apical or subapical area completely heal. May not these scars signify that, when tuberculous infection involves the upper part of the lung, even those individuals with high resistance have considerable difficulty in overcoming the disease? And may not progressing pulmonary tuberculosis occur when the infection occurs in the apical or subapical regions in individuals in whom the balance between the resistance of the soil and the survival of the seed is in favor of the tubercle bacillus?

It is common knowledge that a considerable proportion of the "spreads" of tuberculous infection to the lower two-thirds of the human lung completely resolve. The instances in which this does not happen are in all probability those in which massive infection has occurred. It is also quite probable that tubercle bacilli lodge much more frequently in the lower two-thirds of the lung than is now realized and that in the large majority of such instances the lesions they cause are healed without even being recognized. A progressive basilar tuberculosis, always of grave import, is an infrequent occurrence, especially in the absence of apical or subapical involvement. It would seem, then, that the basic problem confronting those engaged in the treatment of pulmonary tuberculosis is the early recognition, interpretation and control of the apical or subapical foci. These are in the main the most frequent and most persistent of localized tuberculous lesions. It appears that the apical or subapical areas are, with exception, less resistant to progressive tuberculous disease than any other portion of the lung field.

From our experimental studies we are impressed with the fact that the pathological problem of first importance is the control of localized tuberculous legions in the highest portions of the lung parenchyma.

The data which we have presented do not corroborate the explanations which have been advanced for chronic progressive pulmonary tuberculosis in man. The real explanation does not seem to rest upon either an allergic soil or the occurrence of a reinfection. Unless posture brings about an anatomical peculiarity of the lung structure, the anatomy of the lung offers no solution. Our experiments do however further emphasize the seriousness of tuberculous lesions occurring in the higher portions of the lung tissue. Further study is needed to clarify the pathological problem presented in the "adult type" of pulmonary tuberculosis. Since it is possible to produce tuberculous lesions in the rabbit lung which represent the essential features of pulmonary tuberculosis in man,

it would seem that the rabbit offers a medium suitable for the experimental investigation of many of the problems encountered in pulmonary tuberculous infection in man.

CONCLUSIONS

1. The variety of tuberculous lesions obtained in rabbits under various experimental conditions are presented. These are analogous to the localizing, progressing, cavitating, bronchogenic-spreading and retrogressing lesions known to exist in pulmonary tuberculosis in man.

2. Because these lesions have been obtained under experimental conditions in which some factors are known and controlled, it appears to us that the data obtained make possible a more logical interpretation of the type of pathological lesions than is possible for data available from the pathology of uncontrolled and uncontrollable human material.

3. From our data the following points appear to be evident:

a. Allergy does not seem to be the prime reason why localizing tuberculous lesions proceed to cavitation.

b. The alteration of the tissue caused by a primary infection is not the prime reason why in reinfection localized tuberculous lesions cavitate. Similar lesions have been obtained from a first infection.

c. To obtain localizing cavitating lesions it is necessary to have a certain balance between the virulence and dosage of the tubercle bacilli and the resistance of the host plus a localizing of the tubercle bacilli in certain areas of the lung parenchyma.

d. The higher portions of the lung field appear to be less resistant to tuberculous infection than the lower portions.

e. The site of progressing tuberculous lesions can be changed in the rabbit through change of posture.

4. It is suggested that the so-called adult type of human pulmonary tuberculosis is due in large part to the lodging of tubercle bacilli in the less resistant upper units of the lung parenchyma.

5. No definite reason why certain portions of the lung parenchyma are more susceptible to tuberculous infection can be given. Whatever inferences are drawn would be mere conjectures.

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A CORRELATION OF BLOOD COUNTS AND CLINICAL SYMPTOMS WITH RECOVERY FROM TUBERCULOSIS[1]

A Statistical Study

C. H. BOISSEVAIN, A. M. FORSTER AND B. D. GOOD

A considerable difference of opinion exists among clinicians as to what signs are most important in the prognosis of tuberculosis. Since the pioneer work of Webb (1) in 1909 it has been known that a high percentage of lymphocytes is usually associated with recovery in tuberculosis. Others, while admitting the value of a high lymphocyte count, have advocated recovery indices different from the one originally suggested by Webb, which consisted of the sum of the lymphocyte and monocyte percentages. Sabin (2) and her co-workers claim that the monocyte/lymphocyte or M/L ratio is more important than the lymphocyte percentage alone. Rosenthal (3) considers the neutrophiles/lymphocytes ratio as significant, while Medlar (4) makes a correction in this N/L ratio for very high or very low total white counts, and a second correction for high monocyte percentages. Mueller and Broesamlen (5) finally consider the percentage of eosinophiles to be of prognostic significance. All these indices are closely related to each other: the lymphocyte and neutrophile percentages vary inversely: a high lymphocyte percentage is necessarily connected with a low neutrophile percentage. The monocyte/lymphocyte and the neutrophile/lymphocyte ratios vary inversely with the lymphocyte percentage although not in the same manner. If one of the indices is of prognostic value, all must be of value, although to a very different degree. It is the purpose of this study to determine statistically which index is of greatest value.

Routine blood counts at intervals of six months have been made on all patients at Cragmor Sanatorium since 1923. We computed the different indices for each blood count made during the period 1923–1932, and calculated the correlation of these and a selected number of

[1] From the Laboratory of the Colorado Foundation for Research in Tuberculosis, Colorado Springs, Colorado, and from Cragmor Sanatorium, Cragmor, Colorado.

clinical symptoms with the patient's condition on leaving the sanatorium, and with his condition in 1934. The amount of correlation is measured by the correlation-coefficient. In perfect correlation this coefficient becomes ±1.00. An example of very high correlation is for instance that between temperature and pulse-rate. If the increase in pulse-rate were always exactly proportional to the increase of temperature, their correlation coefficient would be +1.00; in actual fact it was +0.743 in our series.

When one variable increases while the other decreases, as, for instance, the lymphocyte and neutrophile percentages do, the correlation coefficient becomes negative. In our series this coefficient was −0.846.

If the factor studied has no effect one way or the other, the correlation coefficient approaches zero.

From the patients at Cragmor during the period 1923–1932 only those were selected for this study whose blood had been examined at least twice; as the routine blood counts are done every six months, these patients had stayed at least that length of time. We judged that a stay of this duration was necessary to make any definite change in the patient's condition manifest. The condition in 1934 was ascertained by sending questionnaires to all patients whose condition at that time was not known. A total of 431 patients with 1,569 blood counts were included in this study; 1,171 counts were made of the blood of patients with far-advanced tuberculosis, 316 with moderately advanced tuberculosis, and 82 with incipient tuberculosis.

Information concerning the clinical condition, temperature, pulse, etc., at the time when the blood count was taken, was copied from the hospital records. The following data were included in our study:

Percentage haemoglobin
Percentage neutrophile polynuclears
Percentage eosinophile polynuclears
Percentage basophile polynuclears
Percentage lymphocytes
Percentage monocytes
Sum of percentage lymphocytes + percentage monocytes (Webb index)
Total white blood count
Total number neutrophile polynuclears[2]
Total number eosinophile polynuclears[2]

[2] Calculated by multiplying percentage from differential count with total white count and dividing by 100.

Total number basophile polynuclears[2]
Total number lymphocytes[2]
Total number monocytes[2]
Ratio monocytes/lymphocytes (Sabin M/L index)
Ratio neutrophiles/lymphocytes
Medlar index
Gaffky number
Amount of sputum
Amount of sputum times Gaffky number
Temperature
Pulse
Physical signs
Gain of weight
Pleurisy pain
Haemoptysis
Nervous condition
Insomnia
Cough
Extrapulmonary tuberculosis

These laboratory and clinical data were correlated with (1) the condition of patients on leaving sanatorium, and (2) the condition of patients in 1934.

To avoid errors by unconscious bias toward some one index, one of us (C. H. B.) computed the indices while the other (B. D. G.) decided whether the patient's condition had improved or deteriorated. It was necessary to give a numerical value to the condition of the patient to enable us to calculate correlation coefficients. We scored as follows: 1 dead; 2 worse; 3 stationary; 4 slightly improved; 5 much improved; 6 arrested; 7 cured. With these values a positive correlation coefficient shows a favorable influence on recovery and a negative value the opposite.

The formula

$$r_{xy} = \frac{\frac{\Sigma xy}{n} - A_x A_y}{\sigma_x \sigma_y}$$

was used for calculating the correlation coefficient where r_{xy} is the correlation coefficient between x and y, Σxy the sum of the products of each pair of x and y, n the number of items in the series, A_x and A_y the

average values for x and y, and σ_x and σ_y the standard deviations (represented by $\sqrt{\frac{\Sigma_{x^2}}{n} - A_x^2}$) of x and y respectively. To determine each correlation coefficient, 1,569 numbers had to be squared, 1,569 products had to be calculated, and 4,707 items had to be added. This was done with the aid of a Hollerith tabulator and several Monroe calculators, that, together with the necessary computers, were put at our disposal by the Cowles Commision for Research in Economics, without whose coöperation and advice this study would have been impossible.

Results

A correlation coefficient smaller than .250 is usually not considered to be statistically significant. The items which show correlations lower than .250 probably have little influence on recovery from tuberculosis. The nearer the coefficient comes to zero the less value must we attach to the item in question. The total number of basophiles, for instance, is universally considered as unimportant in recovery from tuberculosis, and has almost zero correlation (−.002). The probable error provides a test of the significance that we may attribute to a correlation coefficient.[3] A correlation coefficient of .250 based on a series of 1,569 items has a probable error of ±.016. If we reason that our series correlating 1,569 blood counts with the condition in 1934 of 431 patients is really based on only 431 items, then the probable error of a correlation coefficient of .250 is ±.030. This means that, if the correlation coefficient were calculated a great many times for different series of patients, 50 per cent of all the coefficients found would lie between .220 and .280 (.250 ± .030). The probable errors of the correlation coefficients, that are given in table 1, have been calculated on the assumption that the number of patients rather than the number of blood counts constituted the number of items in the series. The largest probable error that we find is ±.033. Since an error of more than seven times the probable error is very rare, occurring less than once in 30 million times, all correlation coefficients over ±.250 in this series are significant.

Of the 33 items studied, 14 showed a correlation coefficient with the condition of the patient in 1934 higher than .250. They are total white count, percentage neutrophile polynuclears, percentage lymphocytes, number neutrophile polynuclears per cmm., percentage lymphocytes,

[3] For a discussion of correlation coefficients, their probable error and a discussion of probability, see: Davis and Nelson, *Elements of Statistics*, Bloomington, 1935, p. 190 and p. 276.

TABLE 1

Correlation coefficients between recovery and laboratory findings

	CORRELATION WITH	
	Condition on leaving sanatorium	Condition in 1934
Haemoglobin	+.217 ± .032	+.197 ± .032
Total white count	−*.386* ± .028	−*.366* ± .029
Percentage neutrophiles	−*.306* ± .030	−*.287* ± .030
Percentage eosinophiles	+.052 ± .033	+.062 ± .033
Percentage basophiles	+.021 ± .033	+.030 ± .033
Percentage lymphocytes	+*.311* ± .030	+*.295* ± .030
Percentage monocytes	+.057 ± .033	+.053 ± .033
Percentage lymphocytes + monocytes	+*.318* ± .030	+*.301* ± .030
Number neutrophiles	−*.320* ± .030	−*.408* ± .028
Number eosinophiles	−.035 ± .033	−.044 ± .033
Number basophiles	−.004 ± .033	−.002 ± .033
Number lymphocytes	−.065 ± .033	−.074 ± .033
Number monocytes	+.015 ± .033	−.014 ± .033
Ratio monocytes/lymphocytes	−.142 ± .033	−.141 ± .033
Ratio neutrophiles/lymphocytes	−*.342* ± .029	−*.323* ± .030
Medlar index	−*.400* ± .028	−*.371* ± .028
Gaffky number	−*.315* ± .030	−*.344* ± .029
Amount sputum	−*.342* ± .029	−*.344* ± .029
Gaffky number × amount sputum	−*.295* ± .030	−.323 ± .030

Correlation between clinical findings and recovery from tuberculosis

	CORRELATION WITH	
	Condition on leaving sanatorium	Condition in 1934
Temperature	−*.415* ± .028	−*.355* ± .029
Pulse	−*.413* ± .028	−*.356* ± .029
Physical signs	−*.269* ± .030	−*.284* ± .030
Gain of weight	+*.276* ± .030	+.248 ± .031
Pleurisy pain	−.184 ± .032	−.163 ± .032
Haemoptysis	−.136 ± .033	−.113 ± .033
Nervous condition	−.242 ± .031	−.219 ± .031
Insomnia	−*.277* ± .032	−.244 ± .031
Cough	−*.486* ± .025	−*.455* ± .033
Genitourinary tuberculosis	−.131 ± .033	−.108 ± .033
Laryngeal tuberculosis	−.012 ± .033	−.008 ± .033
Bone tuberculosis	+.051 ± .033	+.074 ± .033
Intestinal tuberculosis	−.163 ± .032	−.169 ± .033

percentage lymphocytes + percentage monocytes (Webb Index), ratio neutrophiles/lymphocytes, Medlar index, Gaffky number, amount of sputum in 24 hours, Gaffky number times amount sputum, temperature, pulse, physical signs and cough.

Of the clinical symptoms cough takes first place, with a correlation coefficient of −.455, confirming the popular opinion of its importance. Temperature and pulse show almost the same coefficient, as might have been expected: −.355 and −.356. Severity and extension of physical signs, with a correlation coefficient of −.284, is important, but less so than temperature, pulse and cough. Gain of weight (+.248) and insomnia (−.244) just fail to show significant correlation with condition in 1934, but show correlation with the condition on leaving the sanatorium. While gain of weight may have some independent significance, this is not the case for insomnia. Insomnia shows a high correlation (+.719) with temperature, demonstrating that it is usually accompanied and perhaps caused by fever. There is no evidence to show that insomnia, when not caused by high temperature, is harmful for the tuberculous.

Haemoptysis and extrapulmonary tuberculosis had little effect on recovery in this series, reflecting the great improvement in the prognosis of the latter through the use of modern treatment methods.

Among the laboratory examinations the total number of neutrophile polynuclears, with a correlation coefficient of −.408 takes first place: significant values are also found for the total white count (−.366) and the percentage of neutrophile polynuclears (−.287). While the coefficient for the lymphocyte percentage is +.295, the coefficient for the total number of lymphocytes is −.074. The explanation is that the lymphocyte percentage and total white count vary in opposite directions and have opposite significance. In favorable cases we find a high lymphocyte percentage and a low total white count, and in unfavorable cases a low lymphocyte percentage and a high total count. The result is that the total number of lymphocytes per cubic millimetre does not always increase when the lymphocyte percentage increases, and that it may even decrease. If the lymphocytes themselves were active in fighting the tuberculous infection, we might expect that the total number of such cells would be more important than their percentage. Since the total number of lymphocytes is apparently without significance, the lymphocyte percentage must be an indicator of some other factors. These other factors may be the total white count or the neutrophile

percentage which have a very high negative correlation (−.915 and −.846 respectively) with the lymphocyte percentage.

Of the different indices, Medlar's shows a high correlation with the condition of the patient in 1934 (−.371) but the correlation coefficient of the number of neutrophiles is somewhat higher, −.408. On the other hand Medlar's index shows a higher correlation with the condition of the patient on leaving the sanatorium than the number of neutrophiles alone. For all intents and purposes we may consider the Medlar index of equal prognostic value with the number of neutrophiles. This is perhaps not surprising: the three principal components of this index are total white count, percentage neutrophiles and percentage lymphocytes. The value of each of these components depends upon the value of the number of neutrophiles per cmm., directly or indirectly. Indeed, we may say that Medlar used a good deal of ingenuity in first distributing the effect of the number of neutrophiles over his three variables: percentage of neutrophiles, percentage of lymphocytes and total white count, and then recombining them again in his index. The number of neutrophiles per cmm. can be obtained by direct multiplication and its use is to be preferred to that of Medlar's index which requires a special circular slide-rule for its computation. The percentage of monocytes shows no correlation with recovery, and its inclusion in Medlar's index adds only an element of random variation to it.

It is surprising to find that the monocytes, whose importance has been emphasized so much by Sabin and her group, show a nearly zero correlation with recovery, both as regards percentage and total number (+.053 and −.014). The monocyte/lymphocyte ratio has a slightly higher correlation (−.141), obviously due to the inclusion of the lymphocytes in the picture; but even so it is too low to be statistically significant. As we thought it possible that, in the first half of the period considered in this study, insufficient attention had been paid by the laboratory technicians to differentiating between lymphocytes and monocytes, the correlation coefficients for the second half were separately computed but they were practically unchanged from those for the entire period.

This absence of correlation may be due to the fact that most of our material concerned far-advanced cases, with only 82 out of 1,569 counts from incipient cases. It is possible, but not probable, that inclusion of more incipient cases would have changed our results.

A great advantage of the use in prognosis of the number of neutrophile

polynuclears per cmm. over the use of more complicated indices, is that this number can be obtained accurately from the differential count and the total leucocyte count. Workers in different laboratories obtain practically identical results for these counts, while, for instance, the monocyte count shows wide variations. Average correlation coefficients between values found by four workers on 12 slides, counting 500 cells, were:

Type of Cell	*Correlation Coefficient*
Neutrophile polynuclears	+.917
Lymphocytes	+.900
Monocytes	+.493
Eosinophiles	+.460
Basophiles	+.106

The highest correlation is found for the value of the percentage of neutrophile polynuclears. The agreement between different counts is closest for those cells of which most are counted, and becomes progressively less for the rarer types of leucocytes. A sampling error which occurs even when 500 cells are counted makes the value for monocyte, eosinophile and basophile percentage of doubtful value. The lack of agreement for eosinophiles and basophiles must be exclusively due to sampling error as there is no difficulty to distinguish them from all other cells: for the monocytes there is in addition to the sampling error the possibility of a systematic error through failure to distinguish correctly between lymphocytes, polynuclears and monocytes, but it is unlikely to be as large as the sampling error.

As might be expected, both the Gaffky number and the amount of sputum during 24 hours show a significant negative correlation with recovery. It is surprising that the product of the Gaffky number with the amount of sputum does not show a higher correlation than each separately. This value was included as an index of the total number of bacilli eliminated each day. It is not a very good index, as the number of bacilli varies much more rapidly than the Gaffky number, and thus throws our values out of proportion. As a result we do not obtain a higher correlation from the combination than for Gaffky number and daily amount of sputum separately.

Combination of the correlation coefficients: We have now 14 correlation coefficients that are statistically significant: Temperature, pulse, physi-

cal signs, cough, total white count, percentage neutrophiles, percentage lymphocytes, total number neutrophiles, percentage lymphocytes plus monocytes, N/L ratio, Medlar's index, Gaffky number, amount of sputum, and Gaffky number × amount of sputum.

If all the coefficients were mutually independent, it would be possible to include them in an equation which would forecast the fate of the patient with 100 per cent certainty. Unfortunately, most of the coefficients are very closely dependent upon each other, as, for instance, temperature and pulse, or cough and amount of sputum. One of each of these pairs can be omitted without changing the accuracy of the forecast. All the data derived from blood counts are also closely related to each other, and every index that has a significant correlation coefficient is in some way dependent upon the total number of neutrophile polynuclears. As this last one has the highest correlation coefficient, nothing can be gained by considering any of the other data.

By selecting the clinical and laboratory data that seem to be independently variable we can find a regression equation that gives a more accurate prognosis than each datum separately.

From the laboratory we selected number of neutrophiles per cmm., Gaffky number, and amount of sputum. Of the clinical data, temperature, physical signs and cough were included; the only clinical symptom with a correlation coefficient higher than ±.250, but not included in this equation, was pulse-rate, which showed so high a correlation with temperature that nothing could be gained by its inclusion.

In the many different combinations tried, neutrophiles and temperature always appeared as important factors in the calculation of a recovery index. Cough and sputum behaved erratically; in some combinations they appeared as very important factors, while in other combinations they played a very minor rôle. This does not mean that cough and sputum are without significance in prognosis. It means that, of all patients with bad cough and sputum, the great majority also had either high temperature or a high number of neutrophiles per cubic millimetre, and that, mathematically speaking, this could equally well be expressed without including sputum and cough in the equation.

The regression equation that was finally adopted included only number of neutrophile polynuclears per cmm. and temperature. By inserting in this equation the values for temperature, and neutrophiles in a particular case, the most probable value for the condition of this patient after five years can be calculated. The combination of neutrophiles per cmm.

TABLE 2

Recovery index

TOTAL NUMBER* OF NEUTROPHILE POLYNUCLEARS PER CMM.	TEMPERATURE						
	98°	99°	100°	101°	102°	103°	104°
2,000– 2,400	5.0**	4.6	4.2	3.8	3.4	3.0	2.6
2,500– 3,100	4.9	4.5	4.1	3.7	3.3	2.9	2.5
3,200– 3,800	4.8	4.4	4.0	3.6	3.2	2.8	2.4
3,900– 4,500	4.7	4.3	3.9	3.5	3.1	2.7	2.3
4,600– 5,300	4.6	4.2	3.8	3.4	3.0	2.6	2.2
5,400– 6,000	4.5	4.1	3.7	3.3	2.9	2.5	2.1
6,100– 6,700	4.4	4.0	3.6	3.2	2.8	2.4	2.0
6,800– 7,400	4.3	3.9	3.5	3.1	2.7	2.3	1.9
7,500– 8,100	4.2	3.8	3.4	3.0	2.6	2.2	1.8
8,200– 8,800	4.1	3.7	3.3	2.9	2.5	2.1	1.7
8,900– 9,500	4.0	3.6	3.2	2.8	2.4	2.0	1.6
9,600–10,200	3.9	3.5	3.1	2.7	2.3	1.9	1.5
10,300–10,900	3.8	3.4	3.0	2.6	2.2	1.8	1.4
11,000–11,600	3.7	3.3	2.9	2.5	2.1	1.7	1.3
11,700–12,300	3.6	3.2	2.8	2.4	2.0	1.6	1.2
12,400–13,000	3.5	3.1	2.7	2.3	1.9	1.5	1.1
13,100–13,700	3.4	3.0	2.6	2.2	1.8	1.4	1.0
13,800–14,500	3.3	2.9	2.5	2.1	1.7	1.3	0.9
14,600–15,200	3.2	2.8	2.4	2.0	1.6	1.2	0.8
15,300–15,900	3.1	2.7	2.3	1.9	1.5	1.1	0.7
16,000–16,600	3.0	2.6	2.2	1.8	1.4	1.0	0.6
16,700–17,300	2.9	2.5	2.1	1.7	1.3	0.9	0.5
17,400–18,000	2.8	2.4	2.0	1.6	1.2	0.8	0.4
18,100–18,700	2.7	2.3	1.9	1.5	1.1	0.7	0.3
18,800–19,400	2.6	2.2	1.8	1.4	1.0	0.6	0.2
19,500–20,000	2.5	2.1	1.7	1.3	0.9	0.5	0.1

In this table we attach the following meaning to the numbers:

7 cured
6 arrested
5 much improved
4 slightly improved } at the end of five years
3 stationary
2 worse
1 dead

* This number is obtained by multiplying the total white blood count with the percentage of neutrophile polynuclears from the differential count and dividing by two.

$$\frac{\text{Total white count} \times \text{percentage neutrophiles}}{100} = \text{total number neutrophiles}$$

** The following equation was used to calculate these values

$$\text{Recovery Index} = 6.0876 - \frac{\text{temperature} - 96}{2.56769} - \frac{\text{number of neutrophiles per cmm.}}{7074.32}$$

and temperature gave an index with as high a correlation as any other combination.

The correlation coefficient for this neutrophile-temperature index with condition in 1934 was +.461 and with condition on leaving the sanatorium +.520. This is not very much higher than the index for total number of neutrophiles alone (−.408 and −.320). This shows that it is impossible to make a 100 per cent accurate prognosis even by giving proper weight to every clinical and laboratory examination. The correlation coefficients give an indication as to what symptoms are most important for the prognosis, but it is not possible to make the prognosis much more accurate by cumulation of symptoms and signs. In other words, a patient without elevation of temperature has a better prognosis than one with a high temperature, and a patient without sputum has a better prognosis than one who expectorates large amounts, but the prognosis of a patient with both high temperature and large amounts of expectoration is only slightly worse than that of one who has only one of these symptoms.

The correlation coefficients of the neutrophile-temperature index, +.461 and +.520 are not very much higher than the coefficients for cough alone (−.455 and −.486). They have however the great advantage that they can be measured objectively and can be expressed in numbers.

Table 2 shows the most probable prognosis for different values of temperature and neutrophile count. This index would have enabled us to predict the fate of the 431 patients included in this study with considerable accuracy at the time when they were examined.

CONCLUSIONS

1. Correlation coefficients have been calculated for a number of clinical symptoms and laboratory findings with ultimate recovery from tuberculosis.

2. Among clinical symptoms, amount of cough had the highest (negative) correlation coefficient with recovery, −.455.

3. Among the laboratory findings, the total number of neutrophile polynuclears per cmm. had the highest (negative) correlation with recovery, −.408.

4. A combined neutrophile-temperature index was calculated with a correlation of +.461 with recovery.

The authors wish to acknowledge gratefully the generosity of the Cowles Commission for Research in Economics, which put its statistical machinery at our disposal. They are further indebted to Harold T. Davis, professor of mathematics at Indiana University, for much advise and help in the statistical treatment, and to Forrest Danson, statistician of the Cowles Commission for supervising the computation of the correlation coefficients.

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THE ERYTHROCYTE SEDIMENTATION RATE IN ESTIMATING ACTIVITY IN PULMONARY TUBERCULOSIS

WINFIELD O. KELLEY[1]

Many laboratory tests have been devised to aid in the estimation of activity in cases of pulmonary tuberculosis. Among these the sedimentation rate of the erythrocytes has taken an important position as is shown by the great variety of methods used by different workers.

In order to make as many determinations as possible it was decided, at the beginning of this work, to employ the Cutler method (1) which has proved to be simple as well as reliable. Greisheimer, Treloar and Ryan (2) have shown that this compares quite accurately with two other standard methods: the Linzenmeier (3) and the Westergren (4). Some authors (5) (6) have stressed the importance of correcting the sedimentation rate for anaemia. However, in this series of cases no severe anaemia was noted: it did not therefore seem practical to carry out the additional procedure of haematocrit determinations with every test. Masten (7), in a study of cases of pulmonary tuberculosis, was "unable to find any definite relationship between the sedimentation rate and such factors as the red cell count, the hemoglobin and the color index of the blood."

In this study, a series of 290 cases of pulmonary tuberculosis was followed from admission to discharge from the Trudeau sanatorium. Tests were made at approximately six-week intervals, and a total of 1,381 tests was performed. In nearly every instance these tests and the X-ray examinations of the chest were made at the same time. For the first 106 cases total leucocyte and differential counts were also made and compared with the other laboratory findings.

The purpose of this work was to ascertain whether or not the sedimentation test is sufficiently accurate and significant to be adopted as a routine procedure in the estimation of disease activity. It is impossible to determine by laboratory tests the exact clinical condition of a patient, and therefore impossible to have complete agreement between

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any two methods of examination. In spite of this fact, the sedimentation rate as well as the leucocyte count and roentgenogram of the chest were correlated with the examination of the sputum for tubercle bacilli (Gaffky scale), the presence of râles in the chest, and symptomatic activity as determined by elevation of temperature and pulse. These comparisons were made first on the admission examination in every case, and then at the time of discharge. Also the progress of the patients was studied by determining the number of relapses as revealed by the roentgenogram and comparing these with the trends in the sedimentation rate.

Correlation of the Leucocyte Count (WBC), Sedimentation Rate (SR) and X-Ray with Sputum Examination, Presence of Râles, and Symptoms

Tables 1, 2 and 3 include only 106 cases since these were the only ones on which leucocyte counts were made.

TABLE 1

106 CASES	WBC—NORMAL	WBC—SEPTIC	SR—NORMAL	SR—ABNORMAL	X-RAY—INACTIVE*	X-RAY—ACTIVE*
Sputum—0	36 (65.5%)	19	38 (69.1%)	17	39 (70.9%)	16
Sputum—+	17	34 (66.7%)	16	35 (68.6%)	14	37 (72.5%)

* Shadows so interpreted.

The border line for normal leucocyte counts was set at 6,000 neutrophiles per cu. mm. (See previous work of author (8).) The border line for normal sedimentation rates was set at 8 mm. per hour for men and 10 mm. per hour for women, although two extra mm. were allowed when the menstrual period was thought to influence the rate. The roentgenograms of the chest were read by Dr. H. L. Sampson, who interpreted the disease as active or inactive. It is known that the presence or absence of tubercle bacilli in the sputum does not necessarily mean activity or inactivity of disease; nevertheless, a definite correlation was observed.

	per cent
Agreement between sputum and leucocyte count	66.1
Agreement between sputum and sedimentation rate	68.85
Agreement between sputum and X-ray activity	71.7

It was also found that patients with a large number of tubercle bacilli in the sputum (high Gaffky count (9)) were much more likely to have the other findings in agreement. However, with the lower Gaffky counts (between I and II) the correlation was not significant.

Table 2 shows a correlation between moderately coarse râles as determined by the first chest examination after admission and the leucocyte count, sedimentation rate and roentgenogram.

TABLE 2

106 CASES	WBC—NORMAL	WBC—SEPTIC	SR—NORMAL	SR—ABNORMAL	X-RAY—INACTIVE*	X-RAY—ACTIVE*
Râles—0	30 (69.8%)	13	32 (74.4%)	11	34 (79.1%)	9
Râles—+	23	40 (63.5%)	22	41 (65.1%)	19	44 (69.8%)

* Shadows so interpreted.

	per cent
Agreement between râles and leucocyte count	66.65
Agreement between râles and sedimentation rate	69.75
Agreement between râles and X-ray activity	74.45

Table 3 correlates the symptomatic activity as determined by temperature (above 99° for men and 99.6°F. for women) and pulse (above 90 for men and 96 for women) with the same three findings above.

TABLE 3

106 CASES	WBC—NORMAL	WBC—SEPTIC	SR—NORMAL	SR—ABNORMAL	X-RAY—INACTIVE*	X-RAY—ACTIVE*
Symptoms—0	36(57.14%)	27	41(65.08%)	22	40(63.5%)	23
Symptoms—+	17	26(60.47%)	13	30(69.76%)	13	30(69.76%)

* Shadows so interpreted.

	per cent
Agreement between symptomatic activity and leucocyte count	58.81
Agreement between symptomatic activity and sedimentation rate	67.42
Agreement between symptomatic activity and X-ray activity	66.63

If such variable factors as the Gaffky scale, moderately coarse râles, and elevation of temperature and pulse, can be accepted as even fairly reliable guides in the determination of activity, then it must be agreed that the leucocyte count, the sedimentation rate and the X-ray interpretation are still more reliable and accurate because of the consistent agreement seen above.

Since leucocyte counts were not repeated regularly on this first series of 106 cases, the observations thus far recorded were based upon one test for each patient (made within a week after admission to the sanatorium).

For the complete series of 290 cases, the study of leucocyte counts was omitted, but sedimentation rates as well as the other laboratory tests were carried out regularly from admission to discharge. On admission the following observations were noted:

	per cent
Agreement between sputum and sedimentation rate	70.28
Agreement between sputum and X-ray activity	71.65
Agreement between râles and sedimentation rate	73.1
Agreement between râles and X-ray activity	73.6
Agreement between symptomatic activity and sedimentation rate	74.4
Agreement between symptomatic activity and X-ray activity	73.95

Therefore, for the complete series of 290 cases there is a very close correlation between the sedimentation rate and the roentgenogram, in interpreting activity of pulmonary tuberculosis.

In order to study the progress of the patients, the laboratory and clinical examinations made just prior to discharge were studied. Comparison of the sedimentation rate and the sputum examination follows:

Sputum 0 = 189 cases
Of these, 157 cases (83.1 per cent) had normal sedimentation rates

Sputum + = 101 cases
Of these, 39 cases (48.5 per cent) had abnormal sedimentation rates

The reason for this discrepancy in the positive group is the well-known fact that many patients lose all signs of activity before conversion of the sputum from positive to negative.

Comparison of the sedimentation rate with the frequency of moderately coarse râles:

Râles 0 = 189 cases
Of these, 156 cases (82.5 per cent) had normal sedimentation rates

Rales + = 101 cases
Of these, 48 cases (47.5 per cent) had abnormal sedimentation rates

Here we observe that when râles have disappeared the sedimentation rate is most likely to be normal. On the other hand, râles may persist in many cases long after the sedimentation rate has returned to normal.

Comparison of the sedimentation rate with symptomatic activity:

Symptoms 0 = 239 cases
Of these, 198 cases (82.8 per cent) had normal sedimentation rates

Symptoms + = 51 cases
Of these, 40 cases (78.4 per cent) had abnormal sedimentation rates

The agreement here seems to be quite consistent in the positive and negative groups.

At the time of discharge the patients were classified as arrested, apparently arrested, quiescent, improved, unimproved and died, according to the National Tuberculosis Association standards (10).

A correlation of the sedimentation rate with these groups is shown in table 4.

TABLE 4

290 CASES	ARRESTED	APPARENTLY ARRESTED	QUIESCENT	IMPROVED	UNIMPROVED	DIED
SR—Normal	12 (85.7%)	20 (90.9%)	110 (83.74%)	61 (68.5%)	5	1
SR—Abnormal	2	2	21	28	18	8 (88.9%)

It is observed that nearly all of the arrested and apparently arrested groups, and a large percentage of the quiescent group had normal sedimentation rates. In the improved group, the percentage of normal sedimentation rates is as high as should be expected. Due to the standards for classification, the unimproved group does not present a true picture of conditions. Four of the 5 patients with normal sedimentation rates classified as unimproved were minimal cases and did not remain in the sanatorium for a sufficient length of time to be placed in a more favorable group. The fifth patient revealed a questionable X-ray increase which, however, was not confirmed by any other positive findings. Therefore, it is justifiable to state that all of the unimproved cases had abnormal sedimentation rates.

Of 9 patients who died, one had a sedimentation rate of zero a few days before death. This patient was classified as clinically active on admission and had a sedimentation rate of 27 mm. A short time later

he developed signs of meningitis, which gradually progressed concomitantly with a decrease in the sedimentation rate. This phenomenon, which has been noted before (11), is probably a manifestation of a complete loss of resistance, and may be due to a decrease in the fibrinogen content of the plasma. With the one exception just discussed, all of the patients who died had abnormal sedimentation rates.

Many clinicians will agree that the sedimentation rate is of little value in those far-advanced cases of pulmonary tuberculosis in which all the signs of activity are present. However, there is a group of so-called border-line cases in which some test is necessary to warn the physician of an impending relapse. Some of these cases may continue to improve

TABLE 5

		RELAPSES					
		Intrapulmonary increases				Pleurisy	
		Without fluid		*With fluid*		*Or pleural fluid*	
		X-ray inactive on admission	X-ray active on admission	X-ray inactive on admission	X-ray active on admission	X-ray inactive on admission	X-ray active on admission
Sedimentation rate abnormal on admission	Return to normal	0	2	0	1	1	2*
	Increase before X-ray	2	5	0	1	0	0
	Increase with X-ray	1	15	0	4	0	6
	Remained elevated	0	7	0	5	1	8
Sedimentation rate normal on admission	Remained normal	2	1	0	0	4	0
	Increase before X-ray	2	0	0	0	0	0
	Increase with X-ray	3	0	1	1	5	1

* One case of meningitis.

under conservative treatment, while others may require some surgical interference to halt the progression of a slightly active lesion. In this study, an attempt was made to determine whether or not the sedimentation rate was of any value in predicting increase of disease. As a matter of convenience in classification, only increases of shadow in the roentgenogram were considered as relapses.

In the series of 290 cases studied there were 53 relapses as determined by the criterion just mentioned. Thirteen of these increases were complicated by pleurisy with effusion. In addition, there were 29 other cases with pleurisy or pleural fluid although no intrapulmonary increase could be observed by X-ray. The sedimentation rates are correlated with the X-ray findings in table 5.

Of the 53 cases with intrapulmonary increases, 43 were found to have abnormal sedimentation rates on admission, and 42 revealed activity of disease by roentgenogram at the same time. Forty of this last group had abnormal sedimentation rates. Nearly all (92.5 per cent) of these remained abnormal at the same time as or previous to the X-ray increase. The 3 cases with sedimentation rates returning to normal had only slight X-ray increases, and later improved.

Eleven of the 53 relapsing cases had inactive roentgenograms on admission. At this time three of these had abnormal sedimentation rates which became worse on or before the date of the X-ray relapse.

It was observed that the rise in sedimentation rate antedated the development of shadows in the roentgenogram in 9 cases. Clinical symptoms appeared early in a few of these relapsing cases. However, no accurate statistics could be gathered because of so many variable factors.

Pleurisy: In the series of 290 cases, there were 41 which developed pleurisy or pleurisy with effusion. Twenty-nine of these cases had abnormal sedimentation rates on admission. In 33 cases the rates were increased during the time of development of the fluid. It is noteworthy that 75.6 per cent of all the pleural effusions appeared in cases with pneumothorax. It was also observed that 6 cases with disease interpreted as inactive by X-ray nevertheless had abnormal sedimentation rates when pleurisy was present. It may be stated therefore that pleurisy markedly increases the sedimentation rate, and sometimes out of proportion to the extent of intrapulmonary disease.

Weight: A large percentage of the patients in both the active and inactive groups gained weight quite consistently during residence at the sanatorium. Perhaps this is explained partially by the fact that many patients were undernourished previous to admission. Also, the change from an active to a sedentary life was sufficient to aid even the more unfavorable cases in gaining weight. In the total of 290 cases, only 46, or 12.4 per cent, had a net loss of weight from admission to discharge. Nine of these were patients who died, 8 were active cases with abnormal sedimentation rates, but the remaining 29 were inactive cases with normal sedimentation rates. Therefore, 63 per cent of the weight-losers were inactive cases. The only conclusion to be drawn from these statistics is that a loss or a gain in weight does not yield any helpful information about the activity of pulmonary tuberculosis.

Type of sedimentation curve: Cutler (1) has placed considerable emphasis on the graphic method of recording the sedimentation test. This

requires making observations every five minutes for one hour, and plotting the results on a special chart. Cutler differentiates 4 types of sedimentation reaction: the horizontal line (normal), the diagonal line (quiescent), the diagonal curve (slightly or moderately active), and the vertical curve (moderately to markedly active). All of the 1,381 tests performed in this series of cases were plotted and interpreted in this way. All rates, therefore, between zero and 8 or 10 mm. were by definition horizontal lines. It was observed also that rates between 10 and 16 mm. were practically always diagonal lines; rates between 19 and 25 mm. were usually classified as diagonal curves; and rates above 28 mm. were vertical curves. Therefore, a knowledge of the rate per hour would be sufficient to enable one to construct the type of curve with a fair degree of accuracy. In the series of cases studied, the small variations of 2 or 3 mm. in the high rates as well as the slight changes in the types of curves in these cases were of no significance in an estimation of the progress of disease. Since the one-hour reading is sufficiently reliable, it therefore seems unjustifiable to use so much extra time making five-minute readings and plotting these results on a chart, which also requires additional labor.

CONCLUSIONS

1. 1381 sedimentation rates were determined on 290 cases of pulmonary tuberculosis.

2. A close correlation was found between the sedimentation rate and the roentgenogram in a study of the activity of the tuberculous process.

3. In a series of 106 cases, the leucocyte count did not appear to be quite as accurate an index as the sedimentation rate in determining activity.

4. The comparison between the sedimentation rate and the other clinical and laboratory findings, such as sputum, presence of moderately coarse râles and symptomatic activity was definite but not so marked as that between the sedimentation rate and the X-ray findings.

5. The sedimentation rate quite accurately followed the course of disease and in some cases gave warning of relapses before new shadows appeared in the X-ray.

6. In 80.5 per cent of the cases with pleurisy, the sedimentation rate was abnormal.

7. Simplification of technique by making only one reading at the end of an hour would prove quite practical for clinical work.

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THE INFLUENCE OF RADIO ULTRASHORT WAVE THERAPY ON EXPERIMENTAL TUBERCULOSIS IN GUINEA PIGS[1]

DAVID H. KLING AND HENRY M. RUBIN

Radio-short-wave and ultrashort-wave therapy has for several years been employed in the treatment of various conditions. A number of investigations have been published on the action of these high frequency currents on various plant and animal tumors and on bacteria including the tubercle bacillus.

Schliephake (1) claimed a marked sensitivity of tubercle bacilli to ultrashort-wave: for instance, tubercle bacilli exposed in a condenser field of a 4.8-metre apparatus at 53°C. were killed within 10 minutes. Identical cultures heated in a water-bath required 30 minutes for lethal effect at that temperature. In another experiment Schliephake introduced tubercle bacilli into bone-marrow cavities of legs and fingers and into different tissues, and exposed them in an electrical field of the 4.8-metre apparatus. Although during this exposure a temperature of 45°C. was not exceeded the tubercle bacilli were killed. He did not report the time necessary for heatless lethal effect. He reported clinical experience with 10 cases of pulmonary tuberculosis and some cases complicated by pleurisy. He claimed in 8 cases clinical and radiological improvement; but some of the cases had, in addition, other treatment, such as aspirations of effusions and injections. He remarked also the occurrence of focal and general reactions after the treatment, as evidenced by a temporary increase in sputum and temperature.

Stieboeck (2) also reported good results in 11 cases of tuberculosis of skin and fistulae. He had improvement in one advanced case of tuberculosis of the lungs. Schedtler (3), in preliminary experiments with ultrashort waves, gained the impression that the heat effect seems to be the chief factor in ultrashort-wave therapy. He therefore resorted to it in tuberculous processes in which heat, hyperaemization, and anti-inflammatory measures were indicated. He treated 14 cases of pulmonary tuberculosis and dry pleurisy with ultrashort waves of from 3.5

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to 6 m. and obtained favorable results. In 6 cases of wet pleurisy, most of them of tuberculous aetiology, this treatment never produced prompt cessation of the exudation, but 4 refractory cases led to resorption and adhesion, while in 2 other cases the treatment remained ineffective. Three cases of tuberculous empyema were not influenced by treatment. In fistulatous lymph-node processes and in tuberculosis of joints and bones, ultrashort-wave therapy, in addition to open-air-rest cure and codliver-oil treatment, was given. None of these cases showed noticeable improvement. In 4 cases of tuberculous peritonitis, ultrashort waves produced considerable improvement. The symptoms of intestinal tuberculosis likewise were favorably influenced. In view of the fact that patients with pulmonary tuberculosis are highly sensitive to all types of rays, the author was cautious in the application of ultrashort waves to these patients. In tuberculous processes of the larynx and of the eyes, he had thus far gained the impression that the waves promote the healing process, provided the general condition is good and the treatment is continued for a sufficient length of time. Summarizing, the author points out that ultrashort-wave therapy seems to be justified within certain limitations. He was unable to demonstrate any specific action, and thinks that this therapy can be employed whenever intensive heating is desirable. On the basis of these facts, it seemed desirable to study the influence of ultrashort wave in experimental tuberculosis of guinea pigs.

DEFINITION AND TECHNIQUE

The term *radioshort-wave* and *ultrashort-wave therapy* designates the employment of high frequency currents with a range of oscillations between ten to one hundred millions per second, equal to wave-lengths of 30 to 3 metres. The wave-lengths between 10 to 30 metres are commonly called *short waves*. Below 10 metres is the range of the ultrashort waves.

Diathermy works with wave-lenghts around 200 metres. (500,000 to 1,500,000 oscillations per second.) The current is applied directly to the body by metal electrodes and follows chiefly the paths of least resistance. It therefore concentrates in the tissues of greatest conduction, especially in the vascular organs. Tissues of high resistance, on the other hand, like bone and fat are, when possible, avoided. The heat produced depends upon the intensity of current and the resistance.

With the high frequency of the ultrashort wave the direct application

of the metal electrodes as in diathermy is not used because of the danger of burns from the higher voltages. The common technique consists in treatment in the condenser field, where part of the body is placed between insulated electrodes. Here the treated part is a dielectric, subject to the stress of the rapidly changing electric lines of force. The ions within the tissues oscillate in changing directions, producing heat by molecular friction, called *dialectric hysteresis*. As the degree of heat-production depends primarily on the dialectric constant of the tissues and the frequencies employed, it is theoretically possible to heat selectively any desired tissue by employing a frequency which will produce maximum heating. Second, it is possible to heat the exposed part homogeneously by the proper placing of electrodes, as differences in resistance do not affect the penetration quality of the high-frequency electric field as they do the diathermy current. Besides the condenser field, it is possible to employ the magnetic field of the radio short and ultrashort wave. To this end we formed solenoids by several turns of metal bands around an insulating cylinder into which the objects (electrolytes, colloids, animals, parts of the body) are placed. We have used in our experiments both the condenser and magnetic fields of a 6 metre ultrashort-wave Falconer machine of 150 watt output.

MATERIAL

Dr. Emil Bogen, pathologist of Olive View Tuberculosis Sanatorium, Olive View, California, put at our disposal 10 guinea pigs, out of a group of 200 animals simultaneously inoculated with 0.001 mgm. of tubercle culture. These guinea pigs were about 5 months old, males, weighing 14.5 to 20 oz. Three days after inoculation, treatment was started. An average of two treatments was given per week over a period of three months. Each animal received 20 or 21 treatments of 10 minutes each with a Falconer Transtherm of 6 metre wave-length and 150 watt output. Three different modalities were used: (1) General condenser field: Three animals were placed in a 2-litre pyrex beaker and 6- x 8-inch condenser electrodes were placed on the top and bottom. In this way the whole body was within the electric field. (2) Local condenser field: Three by four-inch condenser plates were placed over the back and abdomen of 4 animals, covering the site of inoculation and inguinal lymph nodes (figure 2). A one-half-inch rubber sponge was interposed between the abdomen and the plate. (3) Electromagnetic field (figure 1): Three animals were placed in a 2-litre pyrex beaker. The walls of the

beaker were surrounded by a solenoid consisting of 7 turns of $\frac{3}{8}$-inch copper bands connected to the machine. This created an electromag-

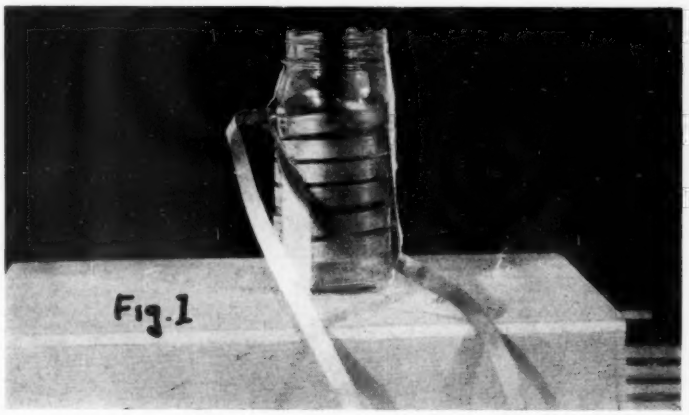

Fig. 1. Showing a solenoid formed by seven turns of a copper band. The free ends are connected with the short-wave machine. Animals are placed in large solenoids of this type.

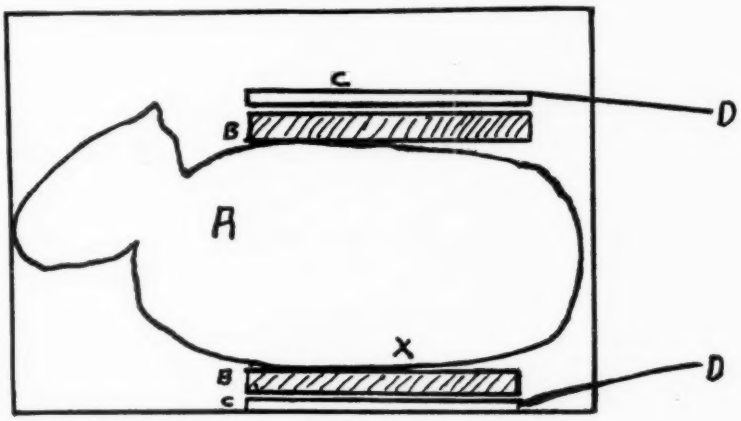

Fig. 2. Showing method of exposing animals by local condenser plates. A: animal; B: rubber sponge (or felt) to prevent burns; C: 3″ x 4″ condenser plates; D: leads to the machine; X: site of inoculation (this as well as the inguinal lymph nodes were always in the field).

netic field within the beaker. Extensive investigations of this modality will be reported elsewhere.

Rectal temperatures were measured before and after each treatment. Resonance, which indicates the most efficient use of the energy, was

established with regularity only in the condenser fields, but not in the electromagnetic. A rise in rectal temperature was accomplished with all modalities, but not during every exposure. The highest rectal temperature was above 110°F. Overheating to this degree was avoided because of the deleterious effects noted in preceding experiments (4). When the temperature was kept below 105°F. the animals were relatively quiet, and after exposure they behaved normally, although considerable water was lost, as noticed by condensation on the beaker walls and thirst indicated after the treatment. Systemic heat was produced with local application over the abdomen as well as by other modalities.

TABLE 1

NUMBER	TEMPERATURE						AUTOPSY TOTAL	REMARKS
	Treatment	Average before treatment	Average experimental temperature	High experimental temperature	High temperature rise	Average temperature rise		
1	G. C.	102.4°	102.9°	105.0°	2.6°	0.45°	9	18 points average 6
2	G. C.	102.0°	103.1°	104.8°	1.8°	0.64°	1	
3	G. C.	102.8°	103.2°	105.5°	3.45°	0.60°	8	
4	L. C.	102.4°	103.5°	105.65°	2.35°	0.91°	6	26 points average 6.5
5	L. C.	102.86°	104.45°	107.3°	3.2°	1.6°	10	
6	L. C.	103.02°	104.9°	108.2°	5.3°	2.1°	4	
7	L. C.	103.1°	104.9°	107.2°	3.8°	1.7°	6	
8	E. M.	102.9°	104.08°	110.°	7.°	2.35°	9	24 points average 8
9	E. M.	103.2°	105.1°	109.°	7.5°	1.9°	10	
10	E. M.	102.4°	103.°	110.°	8.°	2.3°	5	

This was evidenced by rise in rectal temperature and heating of the ears of the animals, although the head was not exposed, and by rise in temperature. All animals survived treatment with no complications. The temperature at the end of the three-month period was elevated 2° to 4°F., which is common during the course of experimental tuberculosis in guinea pigs. The duration of the temperature elevation after treatment is illustrated by the following: *Animal 8:* 14th treatment; temperature before exposure, 102.6°; immediately after exposure, 108.4°; 35 minutes after exposure, 103.2°. Burns were avoided by measures of prevention pointed out in a previous paper (4).

AUTOPSY FINDINGS

After three months the animals were killed as well as the controls. Table 1 gives a summary of experimental and autopsy findings. The autopsy results were made and conditions estimated according to the standards of the pathological department of Olive View by Mr. Loomis. Results were computed on a basis of a possible 16 points for each guinea pig (judged on condition of lymph nodes, spleen, liver, and lungs).

Table 2 gives the frequency and extent of tuberculous involvement of the organs. The average weight of the animals at the beginning was 18.4 oz. At the conclusion of the experiment it was 19.15 oz.

TABLE 2

ORGAN	NUMBER OF ANIMALS AFFECTED	RANGE	TOTAL	AVERAGE
Lymph nodes	10	1–4	27	2.7
Spleen	9	0–2	14	1.4
Liver	8	0–2	9	0.9
Lungs	9	0–3	20	2.0

Abdominal abscesses noted 6 times (due to haemolytic streptococcic infection among both experimental and control animals).

Healing scab noted 3 times.

Scab on ankle (burn ?) noted 1 time.

ANALYSIS OF MATERIAL

The total points of 10 treated animals was 68 as compared with 70 for the controls. No *striking* differences in involvement were noted. The group of three animals treated by General Condenser showed the smallest average of involvement; however, this appears to be purely accidental, and based on one animal, which escaped with slight involvement of one lymph node equal to one point. The highest involvement was shown by the 3 animals treated by the Electromagnetic Field with an average of 8 points. The differences were neither marked nor regular enough to draw any conclusions.

A number of authors, who ascribed the beneficial effect of ultrashort waves to a specific action, stress the importance of giving small intensities which hardly produce a rise in temperature. In this series no difference appears in the progress of tuberculous infection between animals which had a higher heating and those which did not.

Animal 1, treated by the General Condenser Field, having the lowest average rise in temperature of 0.45° had 9 points at autopsy, while no. 2, having only a slightly higher rise of 0.64° had one point. Animal 6, which was exposed to nearly the highest rise in temperature (in Local Condenser Field) with an average of 2.1° and a maximum of 109.2°F. had only four points. At autopsy of the 10 guinea pigs no gross changes were found in the organs which would indicate possible deleterious effects of the ultrashort-wave exposures.

SUMMARY AND CONCLUSIONS

1. In a group of 10 guinea pigs, treated with three different modalities in the electric and electromagnetic fields of a 6-m. ultrashort-wave apparatus, no influence was noted on the development and progression of tuberculous infection and lesions, as compared with a large control group.

2. Weak or strong dosage, as evidenced by a slight or strong rise in temperature, did not seem to have any influence on the development of tuberculous process.

3. With 20 or 21 exposures during the course of three months 10 animals showed no deleterious effects or complications.

4. By careful technique burns were avoided with all modalities applied.

5. While the results of this experiment support the opinion of Schedtler that the eventual beneficial effect on human tuberculosis is apparently due to hyperaemia and heating rather than to any specific action, it must be stressed that our conclusions apply only to the conditions of the experiment and that the number of animals treated is too small to warrant any generalization.

Appreciation is expressed to Dr. Emil Bogen, of Olive View Sanatorium, for placing the materials at our disposal.

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THE EFFECT OF THORACOPLASTY AND PHRENIC PARALYSIS ON THE TOTAL VOLUME OF THE LUNG AND ITS COMPONENT PARTS[1,2]

G. E. LINDSKOG AND I. FRIEDMAN[3]

INTRODUCTION

Phrenic exairesis and thoracoplasty are now widely accepted as therapeutic measures in the treatment of certain types of pulmonary tuberculosis, their beneficial effects being a matter of repeated clinical observation. All types of collapse therapy are necessarily attended by some encroachment upon the respiratory capacity. This is recognized clinically; and may in some cases limit the application of collapse therapy, particularly when the vital capacity is already greatly reduced. Detailed investigation of changes in the various components of the lung volume resulting from these surgical procedures have not yet appeared in the literature,[4] chiefly because a satisfactory clinical method of determining the subtidal or residual air has not been available.

The significance of vital-capacity determinations in thoracic surgery has been stressed by Graham (1) and Yates (2), and their value in guiding prognosis and therapy in pulmonary tuberculosis has been discussed by Myers (3) and Stivelman and Bendove (4). However, only two authors have, to our knowledge, reported the changes in vital capacity after phrenic exairesis. Kochs (5) showed a reduction of vital capacity following operation on the phrenic nerve, and stated that the decrease was less marked and less permanent in younger patients with elastic chest-walls. He stated that the reduction in vital capacity was more constantly observed after phrenic paralysis than after pneumothorax. Gelera (6) reported 6 cases of phrenic paralysis, in four of which the vital capacity decreased from 200 to 700 cc. following operation. The

[1] From the Department of Surgery, Yale University School of Medicine, New Haven, Connecticut.

[2] Aided by a grant from the Research Funds of Yale University School of Medicine.

[3] Davis and Geck Fellow in Surgery.

[4] Since this article was submitted for publication a study on thoracoplasty by C. A. Mc Intosh has appeared in the *Annals of Surgery*.

remaining two showed no change. There are no reported vital-capacity studies following the stages of graded thoracoplasty.

Vital-capacity determinations are notably limited in interpretation because they depend in part upon active coöperation of the subject and are influenced by such factors as postoperative pain and dyspnoea of cardiovascular origin. Moreover, the vital capacity represents only a portion of the total lung volume, and changes in it do not necessarily reflect similar changes in the subtidal component. To arrive at a more complete understanding of the effect of these surgical procedures upon the respiratory mechanism, it would seem desirable to analyze the changes occurring in the various components of the lung volume and particularly in the hitherto neglected subtidal fraction.

The method of Christie (7) affords a technique which is adaptable to the ill and the postoperative patient since it depends upon the quiet rebreathing of a rich oxygen mixture. It has already been applied clinically in a study of the emphysematous chest by Hurtado, *et al.* (8) and by Beecher (9) in a study of postoperative pulmonary complications.

The purpose of this paper is to present the results of total lung-volume studies on patients subjected to graded thoracoplasty and phrenic paralysis in the treatment of pulmonary tuberculosis.

DEFINITIONS

For the purpose of clarity in presentation of the following material, we shall first define the various components of the total lung volume with which we are concerned. An excellent discussion of this subject is found in Christie's paper (7).

Subtidal Volume (functional residual): The air content of the respiratory tract at the conclusion of a normal tidal expiration.

Vital Capacity: The volume of air expired from the maximal inspiratory level to the maximal expiratory level.

Complementary Air: The volume of air inspired from the level of normal inspiration to the maximal inspiratory level.

Supplementary or Reserve Air: The volume of air expired from the level of normal expiration (resting expiratory level) to the maximal expiratory level.

Mean Tidal Air: The average volume of air inspired or expired between the normal inspiratory and expiratory levels.

Total Volume: The air content of the respiratory tract at the maximal inspiratory level (that is, the sum of the complementary, mean tidal and subtidal air).

MATERIALS AND METHODS

Complete lung-volume studies were carried out on 10 patients with pulmonary tuberculosis who presented themselves to the surgical service of the New Haven Hospital for treatment. Three cases were subjected to thoracoplasty in two or three stages, and the remaining seven to phrenic exairesis or crushing.

The determination of lung volume was carried out with the patient always in the supine position and with arms resting at the sides. The head was supported by one or two small pillows. This constant position obviated any volume changes due to altered body posture (10). Fasting conditions were not ordinarily observed, but determinations were not made within two hours after meals. Care was taken not to allow heavy bed clothing to rest upon the chest or abdomen.

The determinations of the subtidal lung volume were carried out according to the oxygen-dilution, rebreathing technique described by Christie (7) in 1932. The details of the method may be obtained in the original article. It will be sufficient to state here that the method depends upon mixing of the nitrogen in the subject's respiratory tract with an air-oxygen mixture in a closed spirometer circuit. The spirometer system is of known dead space (in our case 1260 cc.), and to it is added a controlled volume of oxygen which sustains the metabolism of the patient during the course of the determination (five to seven minutes), the unutilized portion effecting a dilution of the nitrogen in the lung-spirometer system. A gasometric analysis for the nitrogen percentage of the mixed-gas sample in the spirometer bell after the period of rebreathing is concluded allows a calculation of the subtidal pulmonary volume to be made by a simple algebraic equation. In our case, subtidal volume determinations were always made in duplicate or triplicate, and the mean determination taken as an estimate of the true volume.

The vital capacity and its component parts were measured as follows: The patient was connected by an ordinary rubber mouthpiece with lips and nose sealed, as in the Christie method, to a Roth-Benedict recording spirometer. The spirometer was filled with a mixture of air and oxygen. After the patient had breathed quietly for ten or twelve respirations, he was asked to inspire as deeply as possible and then to expire forcibly to the maximal expiratory level. At intervals of 15 to 30 seconds this manoeuvre was repeated until stable maximal values were recorded on the spirometer chart. The complementary and sup-

plementary volumes were all computed from the vital-capacity curve thus recorded. The supplementary air volume was not recorded by measuring the air forcibly expired from the resting expiratory level in a separate expiratory effort.

The results are best presented by reproduction of the protocols of the individual cases which will then be discussed collectively in a following section.

PROTOCOLS

1: Patient J. B.; admitted December 28, 1934; white; married male; aged 50; height 68 inches; weight 118 lbs. The present illness started in 1930, when, after a period of worry over financial difficulties, the patient began to feel run-down. In July, 1933, he had a severe respiratory infection with productive cough, which was finally diagnosed as tuberculosis. He spent eight months in

PLATE 1

FIG. 1. Patient J. B. Roentgenogram of chest December 29, 1934, before thoracoplasty.

FIG. 2. Patient J. B. Roentgenogram of chest after completion of thoracoplasty, March 12, 1935.

FIG. 3. Patient E. E. Roentgenogram of chest, taken prior to admission for thoracoplasty, February 7, 1935.

FIG. 4. Patient E. E. Roentgenogram of chest, taken after completion of thoracoplasty and return to sanatorium, June 6, 1935.

FIG. 5. Patient W. S. Roentgenogram of chest prior to admission for thoracoplasty, May 22, 1935.

FIG. 6. Patient W. S. Roentgenogram of chest after completion of upper thoracoplasty, July 10, 1935.

a sanatorium on a medical regimen, and was discharged in May, 1934, free from symptoms. At the time of discharge he weighed 160 lbs. but soon lost about fifteen. He resumed his work as a travelling salesman. In September, 1934, he suddenly had an haemoptysis followed by three others on successive days. He took to bed, where he remained except for a few hours daily until admission to hospital. He lost progressively in weight, and developed a very annoying and persistent productive cough.

Physical examination revealed a well-developed but emaciated, middle-aged, white male, who appeared chronically ill: temperature 100°; pulse 90; respirations 24; blood-pressure 140/90. The right chest was more prominent than the left, and the respiratory movements of the left chest were much restricted. The percussion note was impaired over the whole left chest anteriorly, and was dull to flat at the left base posteriorly. The breath-sounds and vocal fremitus were increased in intensity over the entire left lung except at the left base where they were somewhat distant. Amphoric breathing was heard over

FIG. 1

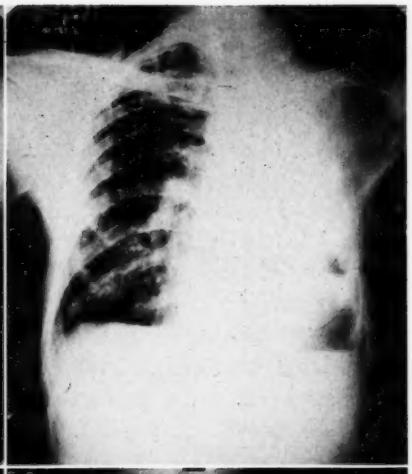

FIG. 2

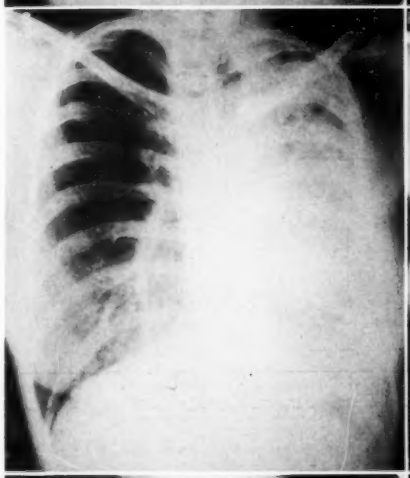

FIG. 3

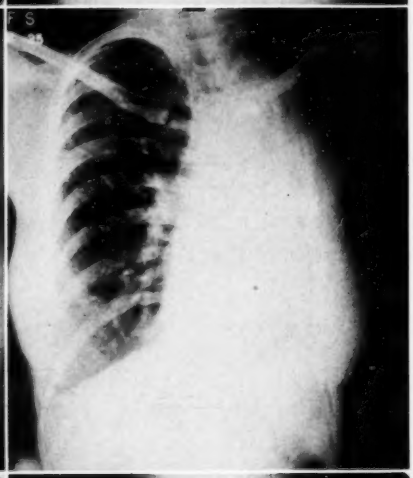

FIG. 4

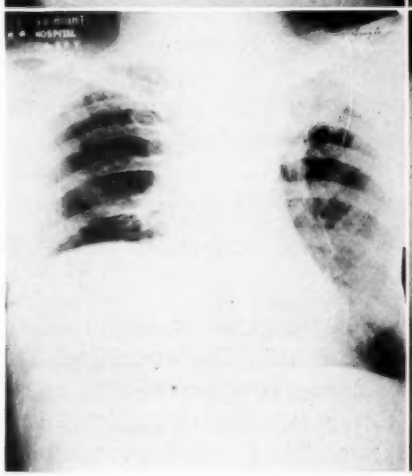

FIG. 5

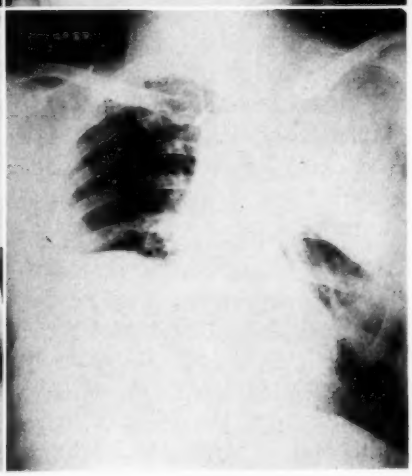

FIG. 6

PLATE 1

the 2nd rib anteriorly, and fine râles over the entire left lung, with occasional râles at the right apex posteriorly. The heart appeared, on physical examination, to be shifted to the left, and a short apical systolic murmur was present. A radiograph of the chest on December 29 (figure 1) revealed the mediastinum to be retracted to the left to a considerable degree, apparently owing to fibrous adhesions. Considerable infiltration was present throughout the left lung field, and a fluid-level noted on the left at the level of the 4th rib anteriorly. Numerous small areas of rarefaction were present throughout the left lung field, some apparently due to antrum formation. The upper third of the right lung field was involved in an infiltrative fibrotic process. The diagnostic impression was bilateral pulmonary tuberculosis.

On admission the blood picture showed a slight secondary anaemia and a normal white count, while the urine was normal. The sputum contained many staphylococci, streptococci and a few acid-fast bacilli on each smear. There was a daily swing of temperature to 101°. On January 8, 1935, a left phrenic exairesis was performed under local anaesthesia. Following this procedure the patient's condition improved progressively. His temperature ranged about the normal without any daily rises, and his irritative cough diminished. On January 14, lung-volume determinations were made and the subtidal volume was 2,070 cc. Repeat determinations were made on February 1, with the following results:

Subtidal	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
1980	2270	600	700	970	3650

On February 2, under avertin and local anaesthesia, a first-stage thoracoplasty was carried out with resection of the 1st, 2nd, 3rd and 4th ribs through a paravertebral approach. Radiographic examination of the chest on February 8 revealed an absence of the greater portions of the upper 4 ribs, with good collapse of the upper half of the left lung. A fluid-level was noted overlying the medial portion of the left clavicle. The trachea did not appear to be as markedly displaced as at the previous examination. The irregular rarefactions were noted again in the lower left lung field. The left dome of the diaphragm was markedly elevated. Lung-volume determinations were carried out on February 9, with the following results:

Subtidal	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
1460	1690	470	550	670	2680

The patient had only a moderate reaction following the first-stage operation, with maximum temperature on the 2nd day of 100.2°. The wound healed well without infection. On February 14, a second-stage thoracoplasty was performed, with resection of large paravertebral portions of the 5th, 6th, 7th and 8th ribs under avertin and local anaesthesia. The patient's reaction to this

stage was also very slight. Radiographic examination on February 26 confirmed the absence of the first 8 ribs on the left in their posterior and axillary portions. There was some shift of the heart to the right; and the right lung field was definitely mottled with a fibrotic infiltration. On February 22, lung volume determinations revealed the following findings:

Subtidal	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
1480	1240	280	460	500	2440

The 3rd and final stage of the thoracoplasty was carried out under the same anaesthesia as before on February 26, with resection of the 9th, 10th, and 11th ribs. The patient's immediate convalescence was satisfactory; and the wound healed *per primum*. Lung-volume determinations on March 7 gave the following results:

Subtidal	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
1350	1420	300	450	670	2470

Roentgenographic examination on March 12 (figure 2) revealed complete collapse of the left chest. A fluid-level was noted in the left lower chest above the dome of the diaphragm with a small air-pocket above it. The right lung field revealed a widely disseminated fibroid type of lesion suggestive of inactivity. Following completion of the thoracoplasty, the sputum was reduced markedly in amount, and acid-fast organisms were found only after considerable search. On March 30, final lung-volume determinations were made:

Subtidal	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
1610	1420	350	500	570	2680

The patient was discharged to a sanatorium on March 31, 1935.

2: Patient E. E.; admitted February 11, 1935; white; single; female; aged 31; height 66 inches; weight 126 lbs. Early in the summer of 1932 the patient noticed loss of weight, strength and appetite. In October, 1932, she developed a paroxysmal cough with expectoration, and two weeks later began to have pleuritic pain in the left lower axillary region. This was associated with a rise in temperature to 103°. The patient was admitted to a hospital where the sputum was found positive for tubercle bacillus; and a diagnosis of left pulmonary tuberculosis was made. Her course was rapidly downhill with a loss of 16 lbs. She was admitted to a sanatorium in December, 1932, at which time a roentgenogram revealed early active pulmonary infiltration in the outer 3rd interspace on the right; and, on the left, apical infiltration down to the 4th rib. Left pneumothorax was started on the 2nd day after admission to the sanatorium, and the patient showed immediate general improvement with lower temperature and slower pulse-rate. She gained 10 lbs. in weight. In April, 1933, it was noticed that she had a small pleural effusion on the left side.

The left lung was approximately 50 per cent collapsed, was adherent in the region of the 2nd rib. During July, the amount of fluid in the left chest increased progressively. Aspiration on August 3 yielded 100 cc. of slightly turbid fluid, a culture of which was negative. On November 28, 400 cc. of slightly cloudy sterile fluid was removed and 500 cc. of air introduced into the left pleural cavity. Pneumothorax was abandoned in December. During the spring of 1934 a large cavity appeared below the level of the clavicle on the left. The effusion in the left pleural cavity was now largely absorbed and there was an area of marked density in the middle lung field. Further collapse was produced by a phrenicectomy on April 4, 1934, following which the dome of the left diaphragm rose about 1 cm. and was completely immobile. After the phrenic operation the patient had a period of reactivation, with elevation of temperature and pulse, considerable malaise, and a loss of 10 lbs. in weight. During the later months of 1934 she began to improve again, showing a gain of weight and increase in appetite, but her sputum remained positive. She was admitted to the New Haven Hospital on February 11, 1935, for thoracoplasty. The positive physical findings were confined to the chest. In the right lung there was slight suppression of breath-sounds over the apex posteriorly with diffuse fine râles after cough in the 2nd and 3rd interspaces in the anterior axillary line. The cardiac apex, located in the 4th interspace, was shifted somewhat toward the left. A soft systolic murmur, not associated with thrill, was heard over the pulmonic area of the heart. The left lung field revealed an impaired percussion note posteriorly, and below the 4th rib anteriorly. Breath-sounds were absent below the 5th rib anteriorly and below the 10th vertebral spine posteriorly; and were faint throughout otherwise. There were diffuse moist râles. The blood-pressure was 110/70 and the pulse 100. The urine was negative on admission. The blood studies showed 5.2 million red cells, 86 per cent haemoglobin, and 13,800 white cells with 77 per cent polymorphonuclears.

Lung-volume studies were carried out on February 12 and 13, with the following results:

Date	*Subtidal*	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
Feb. 12	2110	1560	280	550	730	3390
Feb. 13	1980	——	——	——	——	——

On February 14, a first-stage thoracoplasty was performed under avertin and local anaesthesia. Through a left paravertebral muscle-splitting incision a resection of the entire 1st and 2nd, and a portion of the 3rd ribs was done. The patient stood the operation well. On the 4th postoperative day the vital signs had fallen to the preoperative level. The skin silks were removed on the 5th day and the wound appeared to be healing *per primum*.

On February 22, eight days after the first-stage thoracoplasty, the lung-volume determinations showed the following results:

Subtidal	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
1450	1480	320	470	690	2610

On February 28, under avertin and local anaesthesia, a second-stage thoracoplasty was carried out through a paravertebral incision, and portions of the 4th, 5th, 6th and 7th ribs, varying in length from 12 to 14 cm., were removed. The immediate postoperative convalescence was complicated by the development of lobar atelectasis on the left. There was complete flatness and absence of breath-sounds and a rise of temperature to 104° with several shaking chills. The lung soon began to reaerate; the temperature and pulse were normal on the seventh postoperative day, at which time the wound was healing well and all sutures were removed. On March 8 and 9, measurements of the lung volume gave the following results:

Date	*Subtidal*	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
March 8	1070	1120	180	400	540	2010
March 9	1190	1160	180	460	520	2170

On March 18, a final stage was carried out under the same anaesthesia as before, with resection of portions of the 8th, 9th, 10th and 11th ribs, varying in length from 11 to 14 cm. The patient showed very little reaction to the third stage; the vital signs were not elevated on the second postoperative day. The patient had a slight drug eruption, presumably from amytal. The incision was completely healed on the seventh day postoperatively except for a slight serous drainage near the centre of the wound. On March 25, seven days after completion of the thoracoplasty, lung-volume determinations were made and the following values obtained:

Subtidal	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
1080	1200	260	360	580	2020

Following the third-stage procedure, the patient was placed in a chest-sling of canvas, and supported lying upon the operated side for a considerable portion of each day. She improved in general condition, and ran an afebrile course with a pulse-rate between 90 and 100. Her appetite increased and sputum disappeared. On April 2 and April 11, fifteen and twenty-four days, respectively, after completion of the thoracoplasty, lung-volume determinations gave the following results:

Date	*Subtidal*	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
April 2	910	1080	300	350	430	1690
April 11	950	980	250	350	380	1680

The patient was returned to the sanatorium on April 15, 1935.

3: Patient W. S.; white; male; post-office clerk; aged 51; height 70 inches; weight 189 lbs. The patient noticed a gradual onset of increased fatigability and malaise in 1927. He began to require longer vacations and intervals of rest. In October, 1930, he developed pain in his right chest and began to lose weight. A roentgenogram at this time showed fluid in the right hemithorax and infiltration of both pulmonary apices. He was admitted to a nearby sanatorium in December, 1930, and was an ambulant patient until May, 1931. In May, following the extraction of several teeth, he had fever with increased cough and expectoration of mucopurulent sputum.

In July, 1931, a right phrenicectomy was performed following extension of the pulmonary infiltration to the right base. In November he was transferred to another sanatorium, where physical examination revealed dulness throughout the right chest, more pronounced at the extreme base and at the apex above the 2nd rib, and with bronchial and bronchovesicular breath-sounds and many râles on cough. The left chest showed dulness anteriorly, down to the level of the 3rd rib and posteriorly to the 5th dorsal spine. Bronchovesicular breath-sounds and increased whispered voice were heard just below the clavicle and râles after cough through the entire upper left chest down to the level of the 5th rib anteriorly and the 7th dorsal spine posteriorly. At this time the patient was expectorating daily 20 gm. of mucopurulent sputum, containing 1 to 5 tubercle bacilli per high-powered field. Examination of the blood showed a negative Kahn; 13,300 white cells, and 80 per cent haemoglobin.

With six months of bed-rest, the patient's evening temperature gradually receded to normal, and his weight increased progressively. A series of cold abscesses appeared over the right 5th and 7th ribs and over the right ankle. They were aspirated and the exudate yielded tubercle bacilli. During 1932, his condition improved, and his weight gradually rose from 150 to 178 lbs., but the sputum was still positive. There were three or four episodes of hyperpyrexia, accompanied by chills and suppression of sputum. Serial roentgenograms showed a gradual clearing of the disease in the right lung and the lower part of the left lung, with persistent cavitation just below the left clavicle. In November, 1934, artificial pneumothorax was attempted on the left, but generalized adhesions prevented its success.

The patient was admitted to the New Haven Hospital on May 27, 1935, for left upper thoracoplasty. Lung-volume determinations were first carried out on the day of admission, May 27, and the following results were obtained:

Subtidal	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
2960	2600	730	850	1020	4830

The following day the subtidal volume was repeated, and found to be 3230 cc. The patient's resting expiratory level during these determinations was not a stable one and rendered difficult an interpretation of the respiratory tracings.

On May 29, under avertin and novocaine anaesthesia, a first-stage upper thoracoplasty was carried out through the usual paravertebral muscle-splitting incision. The entire osseous portions of the 1st and 2nd ribs, together with approximately two-thirds of the 3rd rib, were removed. The patient stood the procedure very well and on the 3rd postoperative day his vital signs were normal. On the 7th postoperative day, June 5, lung volume determinations were repeated with the following values obtained:

Subtidal	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
2410	1750	420	840	490	3740

By the 9th postoperative day all sutures had been removed, and the wound appeared to be healing *per primum*. A lighter dressing was applied. The subtidal lung volume was then determined and was found to be 2730 cc.

On June 8, a second-stage thoracoplasty was performed under avertin local anaesthesia, with resection of large paravertebral portions of the 4th, 5th and 6th ribs, the smallest rib segment measuring 12 cm. The patient's reaction to this stage was satisfactory: his vital signs were normal on the third day. He was free from sputum thereafter and the wound healed *per primum*.

Final lung-volume determinations were made on June 15, seven days after the second-stage thoracoplasty, and the following values obtained:

Subtidal	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
2560	1460	230	840	390	3790

He was returned to the sanatorium on June 24, 1935.

4: Patient M. S.; white; single, male; aged 31; height 68 inches; weight 120 lbs.; first admitted to the hospital in March, 1927. Five years before admission he had had a rather persistent cough associated with loss of weight, frequent night-sweats, mild haemoptysis and pain in the left lower chest. Six weeks before admission he had had a similar episode.

Physical examination revealed at both apices fine moist râles and a dull percussion note posteriorly. There was increased whispered voice at the right apex. The sputum was positive for tubercle bacilli. Roentgenograms of the chest substantiated the diagnosis of bilateral apical pulmonary tuberculosis. The patient was discharged to a neighboring sanatorium, where he stayed for four months with considerable improvement and a gain of 12 lbs.

Following his discharge from the sanatorium, he travelled and rested in Europe for a year, during which time he had three large haemoptyses. On his return to the United States, he was hospitalized for one and a half years at a state sanatorium, from which he was discharged with arrested disease. After working a year as a grocer he returned to the sanatorium for an additional two and a half years. He then resumed his work, but three weeks before the final

admission on February 14, 1935, he spat up blood, became very weak, and suffered from a grippe-like infection characterized by generalized soreness and myalgia. At the time of admission, his temperature was 99°, pulse 90, respirations 20, and blood-pressure 100/65. Stereoradiographic examination of the chest revealed a thickening of the hilar and paravertebral trunk-shadows. There was evidence of an infiltrative process in the extremes of both apices, and the overlying pleura was markedly thickened. At the level of the 1st rib on the right was a rounded shadow of rarefaction, measuring 1.5 cm. in diameter, suggestive of cavitation. In the left apex there was a calcified lesion a few millimetres in diameter. The remainder of the lung field appeared clear.

On February 27, under local anaesthesia, the right phrenic nerve was exposed in the neck and crushed with a clamp. Immediate postoperative fluoroscopy of the chest revealed paralysis of the right diaphragm with some elevation. A stereoradiographic examination of the chest on March 26 revealed the diaphragm to lie at the level of the posterior end of the 9th rib. There appeared to have been marked shrinkage of the apex of the right lobe with a decrease in size of the previously described antrum. The left lung showed no change from the previous examination.

Lung-volume determinations were carried out one day prior to the phrenic crushing operation, the day following operation, and after various intervals until June 12. The results are tabulated below:

Date	*Subtidal*	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
February 26 (preoperative)....	2460	2190	320	340	1530	4330
February 28 (postoperative)...	2280	1420	260	340	820	3440
March 5.....	2150	1640	300	340	1000	3490
March 19.....	2010	1850	310	320	1220	3550
April 12.....	1960	2010	370	320	1320	3600
April 27.....	2140	1690	340	280	1070	3490
May 7.....	2410	1800	400	320	1080	3810
June 12.....	2120	1810	340	350	1120	3590

The patient's sputum became negative two months after the phrenic crushing operation and remained negative throughout the remainder of the hospital stay. His clinical progress seemed satisfactory. A repeat radiographic examination on June 8 revealed the dome of the right diaphragm to be still at the level of the 9th rib posteriorly. There was no change in the degree of infiltration at either apex. The patient was discharged to a state sanatorium on June 13, 1935.

5: Patient C. Z.; white; male; truck-driver; aged 29; height 66½ inches; weight 123 lbs. The patient was in good health until June, 1934, when he developed a cold accompanied by fever and pleuritic pain. He suffered persistent productive cough, anorexia and night-sweats, with a weight loss of 15 lbs., and

grew steadily worse, save for a remission in November when he gave up liquor and smoking. During the following months a younger brother with whom the patient had been sleeping was found to have acute pulmonary tuberculosis, and the patient was referred by a visiting nurse to the New Haven Dispensary on December 18, 1934, for observation because of contact.

Physical examination at that time revealed the left lung to be dull throughout, with diminished bronchovesicular breathing and râles over the lower two-thirds. There were signs of cavitation in the left axilla and the sputum was positive for acid-fast bacilli. Stereoradiographic examination of the chest on the same day revealed a widely disseminated infiltrative process throughout the right lung field. The left lung showed a very dense diffuse infiltration, irregular in outline, with numerous cavities in the upper and middle lung fields. The trachea was drawn to the left with a shift of the right border of the cardiac shadow to the midline. A diagnosis of chronic far-advanced bilateral pulmonary tuberculosis was made and the patient was admitted to a sanatorium.

Left artificial pneumothorax was attempted on December 24. A localized collapse at the base was obtained, but was abandoned in one week because of failure to compress the diseased tissue. During the patient's stay in the hospital he had daily swings of temperature from 99 to 101°, of pulse from 90 to 110, and of respirations from 20 to 30. He was troubled by frequent severe cough, and his sputum contained numerous tubercle bacilli on repeated examination. He was admitted to the New Haven Hospital for operation on March 4, 1935. The physical signs on admission were as described above. His temperature was 101.8°, pulse 120, respiration 30. The urine was negative. The blood-count showed 5.3 million red cells and 71 per cent haemoglobin. Studies of the lung volume were made on March 5, with the following results:

Subtidal	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
1900	2170	480	400	1290	3590

A left phrenicectomy was performed under local anaesthesia the same day. The procedure was well tolerated, and fluoroscopic examination on March 6 revealed a complete paralysis of the left diaphragm. Lung-volume studies were repeated on this day, 24 hours after operation.

Subtidal	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
1780	1770	490	340	940	3060

He was returned to the sanatorium on March 6, 1935.

6: Patient J. J.; white; single; male; accountant; aged 29; height 68½ inches; weight 130 lbs. In 1930 the patient had an attack of pleurisy with effusion on the right side; and was observed in a sanatorium for six months during which time there was no positive sputum and no evidence of parenchymal pulmonary tuberculosis. He was well thereafter until three weeks before admission when

he developed an upper respiratory infection with a rather persistent cough. Three days before admission he noticed that his sputum was frequently blood-stained. On the night of February 9, 1935, he had an haemoptysis of approximately an ounce of bright blood. He was found to have a temperature of 102°, and was admitted to the hospital immediately.

There was no history of chronic weight loss, headache, night-sweats, general malaise, loss of appetite, or of contact with other cases of tuberculosis. At the time of admission the temperature was 102.6°, pulse rate 112, respirations 32, and blood-pressure 120/90. The patient did not appear acutely ill; his skin was warm, suffused and somewhat moist, and the pharyngeal mucosa was inflamed. Examination of the chest revealed no definitely abnormal signs except relative dulness to percussion at the left base posteriorly; no râles were heard in either chest. A subsequent roentgenogram of the lungs, however, revealed an infiltrative process involving the entire left lung field. The apex and lower lateral portions of the left lung were not so extensively involved as the remainder of the left side. There was no definite evidence of cavitation. At the level of the right 2nd interspace were thickened pulmonary markings surrounded by small irregular infiltrations. Examination of the blood and urine revealed them to be normal, and acid-fast bacilli were found in only one of 10 sputum specimens. Lung-volume determinations were carried out on February 27, and the following results obtained:

Subtidal	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
3320	2900	600	450	1850	5620

On February 28, under novocaine anaesthesia, a left phrenic exairesis was performed. Fluoroscopic examination of the chest directly following the operation showed paralysis of the left dome of the diaphragm with only slight paradoxical movements. The diaphragm was not markedly elevated. Repeat lung-volume determinations were carried out on the first and sixth postoperative days.

Date	*Subtidal*	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
March 1	3770	2500	610	360	1530	5660
March 6	2610	2740	680	460	1600	4670

The patient experienced no immediate reaction from the phrenic exairesis, and during the subsequent stay in the hospital showed no change in general condition. He was transferred to a sanatorium on March 10, 1935.

7: Patient C. C.; white; single; female; aged 20; height 62 inches; weight 118 lbs. The patient was first examined in April, 1931, because she gave a history of contact with a tuberculous sister. The patient appeared well at that time, and had no symptoms except loss of a few pounds in weight and

occasional sweats at night. Physical examination of the chest revealed no sign of pulmonary disease, but a roentgenogram showed some prominence of the pulmonic markings in the left upper lobe, with a homogeneous increase in density in the left peripheral lung field at the level of the 2nd interspace anteriorly. There was no sputum, but the tuberculin test was strongly positive. The patient was admitted to a sanatorium in August, 1931, and was discharged the following December. She did light work until December, 1933, when she was admitted to a state sanatorium and received pneumothorax treatments. Following discharge in July, 1934, she felt perfectly well until May, 1935, when for the first time a persistent cough appeared. In June the sputum was found to be positive for tubercle bacilli. She was admitted to the New Haven Hospital for treatment on July 16. Physical examination was negative except for percussion dulness at the left apex, both anteriorly and posteriorly. A repeat stereoroentgenogram of the chest showed the hilar shadows to be markedly accentuated with numerous calcified deposits on the left. Fibrotic infiltration was noted in the left upper lobe, with thickening of the pleura along the course of the 2nd left interspace anteriorly. There was also slight fibrotic infiltration in the right upper lobe in the 1st interspace, with increased marking of the pulmonic trunks in the paravertebral region. The patient showed a daily swing of temperature to 100 degrees with slight elevation of pulse rate. Lung-volume studies were first made on July 23, and the following values obtained:

Subtidal	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
2490	2780	600	400	1780	4670

On July 24, a left phrenic-crushing operation was carried out under local anaesthesia. Fluoroscopic examination immediately after the operation revealed complete paralysis of the left diaphragm with slight paradoxical movement. The patient showed no immediate or late postoperative complications. Lung-volume studies were repeated the day following operation and after various intervals until discharge.

Date	*Subtidal*	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
July 25	2260	2270	480	400	1390	4050
August 1	2230	2330	590	420	1320	3970
August 15	2190	2250	510	380	1360	3930

Following the phrenic operation the cough persisted without significant change. The sputum was positive on repeated examinations. The daily temperature range, however, was more nearly normal. There was no significant change in weight. The patient was discharged to a state sanatorium on August 16, 1935.

8: Patient E. M.; white; single; female; factory-worker; aged 21; height 63½ inches; weight 103 lbs. The patient was first admitted to the New Haven

Hospital on March 23, 1935. Three weeks prior to admission she contracted a severe cold accompanied by malaise, productive cough and pain in the left upper chest. She continued to work for one week, and noted a loss of approximately 15 lbs. in weight. She took to bed in the second week because of general weakness, and about ten days before admission had a frank haemoptysis.

On physical examination at time of admission the positive findings were confined to the left lung. The respiratory excursions of the left hemithorax were somewhat limited. There were signs of cavitation in the upper third of the left lung field, with numerous râles to the midaxillary line. A stereoradiographic examination on March 25 revealed displacement of the trachea and heart toward the left side. The entire left lung field showed increased density, through which was visualized extensive pulmonary infiltration characterized by coarse, coalescent parenchymatous mottling. The extreme left pulmonary apex was the site of a very large cavity, practically filling the circle of the 1st rib and extending below the anterior end of this rib. The cavity measured approximately 5 cm. in its greatest diameter, and was surrounded by a broad zone of increased density. The right lung field showed compensatory emphysema and several small areas of calcification. The sputum was found positive for tubercle bacilli.

Numerous attempts were made at induction of pneumothorax collapse on the left side, but the mean pleural pressure always rose rapidly with injection of only 100 or 200 cc. of air, and on April 24, there was no demonstrable pneumothorax. The patient was having a daily swing of temperature to 100 or 101°, and cough persisted with much mucopurulent sputum. Consequently, a left phrenic exairesis was advised. Lung-volume determinations were first made on May 9, and repeated on May 10. The following values were obtained:

Date	*Subtidal*	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
May 9	2040	1690	340	370	980	3390
May 10	1970	1740	260	350	1130	3450

On May 11, under local anaesthesia, a left phrenic exairesis was performed. The patient's clinical condition was not immediately influenced by the operation. Lung-volume studies were repeated on the 1st, 7th, and 14th days after the procedure and the following values were obtained:

Date	*Subtidal*	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
May 12	1840	1420	200	320	900	3060
May 18	1850	1660	390	360	910	3120
May 25	1870	1760	420	360	980	3210

The patient's condition gradually improved. The amount of sputum diminished, and the daily maximum temperature was in the neighborhood of 100°. The patient was transferred to a sanatorium on May 28, 1935.

9: Patient H. C.; white; married; female; housewife; aged 54; height 63½ inches; weight 121½ lbs. Twenty-two years prior to the present admission the patient had fibrinous pleurisy, and for many years afterward her condition was frail. The present illness began insidiously in July, 1934, with productive cough, subsequently associated with weakness, palpitation, night-sweats and loss of 20 lbs. in weight. She was admitted to a nearby sanatorium on January 26, 1935, at which time examination revealed a markedly contracted left lung with dulness and râles over the entire side and signs of extensive cavitation in the left upper lobe. Signs on the right side were limited to râles at the apex. A fracture of the 7th rib was noted on the right side. The heart was shifted far to the left, and a systolic murmur was heard at the apex; the blood-pressure was 130/74. The urine, blood count, and sedimentation tests were normal. The Kahn test was negative. During the patient's stay in the sanatorium there were daily swings of temperature from 96 to 99°, pulse from 80 to 100, and respirations from 18 to 22. She raised daily about 20 cc. of mucopurulent sputum containing numerous tubercle bacilli. The patient gained 2 lbs. during three weeks of bed-rest at the sanatorium. Artificial pneumothorax was attempted twice but no pleural space could be located, and the patient was transferred to the New Haven Hospital on February 19 for phrenic exairesis. The temperature on admission was 99°, the pulse 96, and respirations 20. The physical findings were essentially the same as noted above. Determinations of the lung volume were made prior to operation on February 20, with the following results:

Subtidal	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
1650	1800	340	380	1080	3110

A left phrenic exairesis was done under local anaesthesia on the same day. The operation was well tolerated. On February 21, the left diaphragm was observed fluoroscopically to be paralyzed, and lung volume determinations showed the following results:

Subtidal	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
1530	1470	310	380	780	2690

The patient was returned to the sanatorium on February 22, 1935.

10: Patient S. D.; white; single; female; stenographer; aged 29; height 63 inches; weight 108 lbs. This patient was transferred to the New Haven Hospital from a nearby sanatorium on May 9, 1935. Seven years previously she was hospitalized for three months because of left-sided pneumonia followed by pleurisy with effusion. Tuberculosis was diagnosed and she was transferred to a sanatorium where she remained for the ensuing year. Her progress was satisfactory and at the time of discharge her disease was considered to be

arrested. Her condition remained satisfactory until April, 1934, when she developed a severe upper respiratory infection. She was advised to reënter the sanatorium but refused. A tonsillectomy was done in August, 1934. Healing was slow, and was followed by aphonia, pain in the left chest, fever, cough, expectoration, and progressive loss of weight. The patient was admitted to a sanatorium on April 23, 1935. Examination at this time revealed a normal temperature, pulse 104, respirations 24, and weight 99 lbs. There was ulceration of the right vocal cord posteriorly, and examination of the chest revealed bilateral apical lesions with cavitation on the left. The sputum was positive for tubercle bacilli. The Kahn test was negative. A diagnosis of chronic pulmonary tuberculosis, far advanced, and tuberculous laryngitis was made. Artificial pneumothorax was attempted on the left side on April 29, but was unsuccessful, and on May 9 the patient was transferred to the New Haven Hospital for phrenic neurectomy. A left phrenic exairesis was done under local anaesthesia on May 10. Fluroscopic examination on May 11 revealed a complete paralysis of the left diaphragm, and the patient was discharged to the sanatorium. Estimations of the lung volume were made on May 10, just prior to the operation, and on the next day with the following results:

Date	*Subtidal*	*Vital capacity*	*Reserve*	*Mean tidal*	*Complementary*	*Total volume*
May 10	1710	1380	140	360	880	2950
May 11	1510	1320	280	340	700	2550

DISCUSSION

A study of the protocols in the 7 cases upon whom phrenic paralysis operations were performed reveals in six a fall in subtidal volume on the first postoperative day. The decrease varied from 120 to 230 cc. with a mean of 170. In three of these cases further determinations were made on the sixth to eighth postoperative days and showed reductions of 155 to 310 cc. from the preoperative values, the mean being 240. For these 9 determinations the average postoperative diminution in subtidal volume was 190 cc.

It has been our experience that the precision of the method for estimation of subtidal volume varies with different subjects, depending chiefly upon the stability of the resting expiratory level during the course of the determination. Hence, it would be misleading to assign significance in all cases to changes in excess of an arbitrary value. We have, therefore, computed the significance of observed changes according to the "t" test of R. A. Fisher (11), which takes into consideration the variance of

control observations in individual cases.[5] The values of "P," used in the usual sense (11), are given in table 1, and indicate that the variation in control determinations renders it difficult to attach great statistical significance in certain cases to changes of the small magnitude usually encountered. Nevertheless, the finding of similar changes in 6 of the 7 patients studied clearly indicates that a small but appreciable diminu-

TABLE 1

PATIENT	TIME	SUBTIDAL VOLUME	POST-OPERATIVE CHANGE	VITAL CAPACITY	POST-OPERATIVE CHANGE	CRITERION OF SIGNIFICANCE P
4 M. S.	Preop.	2460		2190		
	Postop. 1 day	2280	−180	1420	−770	0.2 to 0.1
	Postop. 6 days	2150	−310	1640	−550	0.05 to 0.02
5 C. Z.	Preop.	1900		2170		
	Postop. 1 day	1780	−120	1770	−400	0.6 to 0.5
6 J. J.	Preop.	3320		2900		
	Postop. 1 day	3770	+450	2500	−400	0.05 to 0.02
	Postop. 6 days	2610	−710	2740	−160	0.02 to 0.01
7 C. C.	Preop.	2490		2780		
	Postop. 1 day	2260	−230	2270	−510	0.05 to 0.02
	Postop. 8 days	2230	−260	2330	−450	0.02 to 0.01
8 E. M.	Preop. (mean)	2000		1710		
	Postop. 1 day	1840	−160	1420	−290	0.2 to 0.1
	Postop. 7 days	1850	−150	1660	−50	0.5 to 0.4
9 H. C.	Preop.	1650		1800		
	Postop. 1 day	1530	−120	1470	−330	0.2 to 0.1
10 S. D.	Preop.	1710		1380		
	Postop. 1 day	1510	−200	1320	−60	0.2 to 0.1

tion of subtidal lung volume may be regarded as a characteristic effect of phrenic paralysis.

In one patient (protocol 6) results of a widely discordant nature were

[5] The function "t" is computed from the difference of the observed means and an estimate of the standard deviation of this difference. The criterion of significance, P, represents the probability that, if the two samples were taken at random from the same population of normal distribution, a value "t" would be obtained numerically exceeding that observed. Hence, the smaller P indicates greater significance.

observed. There was a striking rise in subtidal volume on the first postoperative day followed by a profound decrease, as measured on the sixth postoperative day, to a point far below the preoperative level. There was no clinical evidence of active pleurisy, transient atelectasis or abdominal distention, and we are at a loss to explain the observed sequence of changes; particularly since control determinations were in close agreement, as indicated by the low values of P.

All 7 patients exhibited a decrease in vital capacity on the first postoperative day varying from 60 to 770 cc. with a mean of 395. In four instances, determinations were repeated about a week later, and showed return toward the preoperative values averaging 190 cc. The ratios of the volume decrease in subtidal air and vital capacity reveals no constant relationship.

An analysis of the data presented by the 3 cases of graded thoracoplasty shows strikingly that the maximal reduction in subtidal volume occurred after the first stage, which involved resection of the upper 3 or 4 ribs. On the seventh or eighth day following the first stage, the observed decreases were all over 500 cc. These exceeded by far any diminutions noted after the lapse of a similar time-interval following the second-stage operation. In fact, one patient (protocol 1) showed an insignificant rise in subtidal volume at this time (20 cc.). In the 2 patients who had third-stage procedures, the further decreases were but 50 and 130 cc.

The reduction in lung volume induced by collapse is probably obscured to a variable extent by subsequent compensatory changes in the uncollapsed (particularly the contralateral) lung field. It would seem, therefore, that the collapse effect would be best demonstrated by measurements made soon after the operative procedure. On the other hand, Beecher (9) has shown that in patients subjected to laparotomy there is a prompt decline in subtidal lung volume, followed by a return toward the preoperative level from about the fourth day through the second week. A similar transient effect may perhaps occur after any major surgical procedure. From this point of view it would appear that a postoperative recovery period of several weeks should be allowed for comparable measurements. As a compromise, we have made determinations following each stage at the end of the first postoperative week.

The diminution in subtidal volume following the first-stage operation was accompanied in each case by a decrease in vital capacity, marked in

two patients. The second stage resulted in further but smaller decreases.

The reduction in vital capacity occurred chiefly at the expense of the complementary and reserve fractions which together represent the volume of air available for unusual respiratory demands. If the reserve-air volume at various stages be divided by the sum of the corresponding complementary and reserve-air volumes, ratios are obtained which appear to vary but little for each individual patient. This indicates that the tidal respirations occupy approximately the same relative position with regard to the maximal inspiratory and expiratory levels. The most marked deviation from this relationship occurred in a patient (protocol 2), in whom, after completion of the thoracoplasty, the subtidal volume was reduced to 45 per cent of its preoperative value. In this case the third-stage operation was followed by proportionately less encroachment upon the reserve-air volume than upon the complementary. Had both been reduced in equal proportions a greater diminution in subtidal volume would have resulted.

SUMMARY

1. Complete lung-volume studies have been made on 10 cases of pulmonary tuberculosis subjected to surgical therapeutic procedures, three being graded thoracoplasties and seven phrenic paralysis.

2. In 6 of 7 patients phrenic paralysis resulted in a decrease of subtidal volume averaging 170 cc., as measured on the first postoperative day. At this time all seven showed a diminution in vital capacity, averaging 395 cc. Measurements thereafter showed a tendency for the vital capacity to return to the preoperative level.

3. In 3 cases of graded thoracoplasty the first stage, involving resection of the upper 3 or 4 ribs, was followed by the most marked decrease in subtidal volume and vital capacity.

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PULMONARY CYSTIC DISEASE[1,2]

WILLIAM C. POLLOCK

Pulmonary cystic disease is one of the rarer of lung conditions encountered in medical practice. Although over 120 cases have been reported in the literature, individual physicians have been able to observe relatively few patients suffering from cystic disease of the lung.

We have had an opportunity to observe three patients with definite cystic formation in the lungs, one of them for a period of ten years, which has enabled us to make observations from the viewpoint of progression or nonprogression of the disease.

We have encountered several patients with localized pulmonary emphysema sufficiently far advanced to resemble cystic disease of the lung. These are examples of acquired pulmonary emphysema. In some of these patients there were apparent aetiologic factors of a character sufficient to produce the extreme emphysematous condition.

Numerous theories have been advanced as to the aetiologic factors responsible for the formation of pulmonary cysts. Most of these theories, however, postulate some embryonic developmental defect of the bronchial tree. It is for this reason that pulmonary cystic disease is usually classified as *Congenital Pulmonary Cystic Disease.*

In our 3 patients presenting definite pulmonary cystic disease, we concluded that the formation of the cysts resulted from developmental defects of the bronchus or bronchi supplying the particular involved lobe or lobes. This conclusion was reached after bronchoscopic and bronchographic observations. These bronchial developmental defects were noted in adults, and the duration of the pulmonary cystic condition was unknown. It would seem rather difficult to determine whether the cysts of the lungs were congenital or acquired as a gradual development resulting from the congenital abnormality of the bronchus or bronchi.

We have observed the development of localized pulmonary emphysema with bleb-formation sufficiently large to approach a cystic condition. It is possible that some of the patients diagnosed as congenital

[1] From the Medical Service, Fitzsimon's General Hospital, Denver, Colorado.

[2] Published by permission of The Surgeon-General, U. S. Army.

pulmonary cystic disease have acquired the cystic condition. It is also possible that the condition is not only an acquired one, but one of gradual transition from localized pulmonary emphysema (blebs) finally to form a cystic condition. Patients with cystic disease usually are not observed until the pulmonary cysts are sufficiently large to reduce the vital capacity of the lung and the symptom of dyspnoea is present. There is usually, in adults, a history of very gradual increase in dyspnoea covering a period of months or years.

Though we are inclined to believe that our cases have resulted from congenital bronchial defects, we are unable to ascertain the duration of the pulmonary cysts. One must, however, admit that other aetiologic factors may also produce pulmonary cysts. Congenital bronchiectasis or peribronchial pressure from an abnormal growth may, by its mechanical pressure, sufficiently reduce the lumen of the bronchus as to restrict the expulsion of the inspired air which in time may produce lung cysts.

Pulmonary cystic disease is usually initially diagnosed as localized spontaneous pneumothorax. Cystic disease, however, should be readily differentiated from pneumothorax by careful X-ray interpretation, bronchoscopy, bronchography, thoracentesis with lipiodol instillation, and possibly by induced pneumothorax. Each of the above procedures should yield diagnostic information and usually one or two procedures will suffice to definitely establish a correct differentiation. It is believed that all patients with pulmonary cystic disease should have a careful bronchoscopy followed by bronchographic study. These procedures permit conclusions as to the aetiological basis of cystic disease of the lung and enables one to determine the presence or absence of a foreign body causing an obstructive emphysema.

Thoracentesis, with the insertion of a long, small-calibre needle into the cystic area, followed by the instillation of a small amount of lipiodol, has given us much additional information. By this procedure we have been able to demonstrate the presence of cyst-walls too delicate to be visualized in the X-ray film.

It is by this procedure, and this alone, that we have been able to demonstrate that certain areas, which appeared to be a large pulmonary cyst, were, in fact, a group of smaller cysts. Large single cysts do exist, as proved by autopsy findings, but these are in the minority. Our study has convinced us that in the vast majority of patients considered to have large lung cysts the apparent large cysts are merely collections of smaller

ones possessing very thin walls. Estimation of the size of these cysts may be obtained by making X-ray films of the patient in various positions following the instillation of lipiodol by thoracentesis. We have been able to visualize and estimate the size of emphysematous blebs in marked localized pulmonary emphysema resembling a cystic condition. In one patient the procedure caused a small area of pneumothorax, but the air was readily absorbed and the patient was not aware of the condition. The particular area is more or less functionless as far as blood-aeration is concerned, and no functional disturbance should accompany the accident of localized pneumothorax. In our patients with cystic disease we have not encountered a free pleural space, as there has always been pleural symphysis near the termination of the cystic area.

The X-ray film aids materially in differentiating lung cysts from localized spontaneous pneumothorax. By careful X-ray interpretation one is often able to differentiate the two conditions. Both conditions enable us to visualize a remarkable rarefied area. Both conditions may present fine, dense lines traversing the apparent space. In spontaneous pneumothorax these lines are straight, and may be traced from their visceral pleural attachment to a parietal pleural attachment. These lines invariably are straight because they are taut and they widen to a wedge-shaped area at their attachment. The fine, dense lines visualized in cystic disease are the borders of cysts or group of cysts and are not taut. They usually arise from the region of the mediastinum and run downward, outward and upward, producing a long, sweeping curve. Some one line may appear rather straight but, if a ruler is placed along the line, its straightness will be seen to be only apparent. These curved lines do not present pleural attachments and, therefore, present no broadening at their termination. In fact, they may be seen to gradually fade into invisible structures.

The X-ray film does not visualize, in cystic disease, pathological lesions such as in tuberculosis which are so frequently readily seen in spontaneous-pneumothorax cases.

In spontaneous pneumothorax the compressed lobe with a distinct visceral pleural border is usually seen, while this is not true in cystic disease. The mediastinum is usually more displaced in pneumothorax, but, since some slight displacement is observed in cystic disease and since in spontaneous pneumothorax the mediastinum may be relatively fixed,

this cannot be used as a differentiating point though it may aid somewhat. Both conditions may present an increase in the diameter of the involved hemithorax.

The history may aid, to some extent, in diagnosis, as frequently in cystic disease the symptom has only been that of gradually increasing dyspnoea, while in spontaneous pneumothorax the onset is sudden, with dyspnoea and pain. In some patients who complain of dyspnoea, cough, chest discomfort, fatigue and loss of weight, the symptoms may be from either condition. The physical signs of the two conditions may be identical. Both conditions may present absence of breath-sounds, decreased fremitus, decreased expansion of the hemithorax, decreased vocal resonance, hyperresonance, and plus coin sound.

In cases of tuberculosis with spontaneous pneumothorax, râles may be elicited in involved portions of the lung or lungs uncollapsed by the pneumothorax. Additional information, such as history of haemorrhage, long duration of cough, and expectoration of a progressive character and tubercle bacilli in the sputum, aids materially in diagnosis.

The tuberculous individual who develops a spontaneous pneumothorax, in the vast majority of instances, knows that he suffers from pulmonary tuberculosis. The patient with pulmonary cystic disease may have his pulmonary condition discovered accidentally by routine X-ray film while in the hospital for some illness other than a chest condition.

Artificial-pneumothorax induction as a diagnostic procedure has been carried out with success. This procedure is usually unnecessary for the establishment of a definite diagnosis. In one of our patients in whom it seemed impossible to instil lipiodol into the bronchus of the upper lobe, pneumothorax was induced and the visceral pleural lung margin was definitely visualized in the X-ray film. This step positively differentiates cystic disease of the lung from spontaneous pneumothorax. After the pneumothorax was induced and an X-ray film made, the air was immediately aspirated from the intrapleural space. The procedure may be complicated by the rupture of the wall of a subpleural pulmonary cyst with the formation of a valve-type fistulous tract, thus continuing the existence of the pneumothorax. This accident may prove troublesome in the case of an emphysematous bleb of the lung, but in pulmonary cyst the lessened amount of air entering the cyst minimizes the severity of the complication.

In patients with pulmonary cystic disease it appears that, regardless

of the duration of the disease, contralateral pulmonary hypertrophy is not observed. This is an interesting observation when one considers that, in other conditions in which the function of one lung is greatly diminished, contralateral pulmonary compensatory changes are so often noted. In extensive fibrosis, fibrotic tuberculosis, artificial pneumothorax and in thoracoplasty the opposite lung usually undergoes compensatory changes. In these conditions, breathing in the compressed, collapsed or atelectatic portion of the lung is rather bronchial in character. Inspired air does not expand the lung parenchyma. In cystic disease a portion of the inspired air actually enters the cystic areas and therefore less pressure is exerted in the contralateral lung during the inspiratory phase.

Case Histories

U. M.: White; female; aged 37 years when first admitted to hospital. Negative history as to any previous illness. Very active athletic type; played considerable tennis, as well as doing a great deal of mountain climbing. During 1924–1925, developed series of colds, and, during these attacks, experienced considerable difficulty in getting up sputum. During the summer of 1925, again attempted to play tennis, but found that physical exertion produced dyspnoea and great fatigue. About this time, developed acute tonsillitis and consulted a medical officer. During general physical examination, the officer detected a difference in mobility of the two hemithoraces; and this, with unusual pulmonary findings, led to making an X-ray film of the chest. From the X-ray film a diagnosis of spontaneous pneumothorax was made.

Admitted to Fitzsimons Hospital in February 1926, which was ten months after the first X-ray observation, yet no changes were noted in the size of the apparent pneumothorax space. For this reason the diagnosis of pneumothorax was disputed. Bronchoscopy and bronchography resulted in the conclusion that the bronchi of the upper one-half of the left lung were apparently much underdeveloped. Lipiodol was instilled into the cystic area by thoracentesis, and the X-ray film following this procedure outlined the borders of the various cystic area. The large rarefied areas were found to be made up of numerous cysts varying in size. By use of lipiodol in this manner we were able to outline fine cyst-walls in areas that appeared to contain no structures whatsoever. Plates made in various positions allowed the lipiodol to shift in position and to demonstrate borders of the various cysts.

X-Ray: The X-ray film made in 1926 presents a marked rarefication of the upper two-thirds of the left lung field. Traversing this rarefied area are numerous fine dense lines. One of these lines extending from the region of the hilum to the 1st intercostal space at the level of the clavicle is straight.

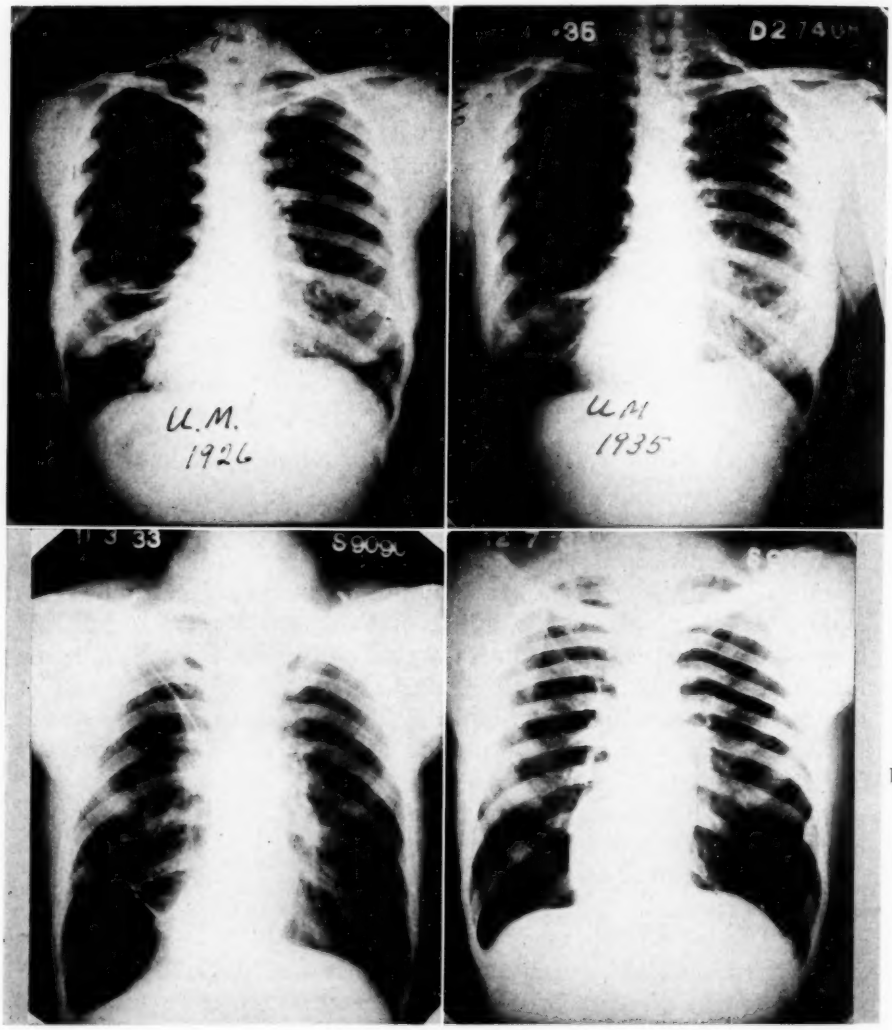

FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 1. U. M. X-ray of chest taken in 1926. Multiple pulmonary cysts on left.

FIG. 2. U. M. X-ray of chest, taken in 1935. Note that the condition has remained unchanged during a period of almost ten years.

FIG. 3. N. B. Localized emphysema of left base, following, pulmonary reëxpansion after localized spontaneous pneumothorax.

FIG. 4. H. H. Localized pulmonary emphysema, 1933. Penetrating wound producing localized pneumothorax in the same area, 1932.

Other lines traversing the region of the upper lobe show some curving. Below this area all lines are of long sweeping curves. There is increased density of the lower one-third of the left lung field. The diameter of the left hemithorax is 2 cm. greater than that of the right. Mediastinum approximately normal as to position, being very slightly toward the right. X-ray film, made in 1935, shows no change from that of 1926. The area of rarefication has not increased or diminished, and every line traversing the hemithorax is identical with those observed in the 1926 film.

Discussion: It is rather striking that this athletic-type adult should, within a very few months, become totally unable to indulge in any form of physical exertion. When the X-ray was made of the chest in 1925, it was found that the upper two-thirds of the left lung structure had been replaced by a cystic condition.

The lipiodol instillation gave much additional information in this case. In areas apparently devoid of all structure we were able to demonstrate that the particular area was made up of numerous cysts with walls too delicate to show on the X-ray film. This patient had taken part in athletics in both high-school and in college, had done rather strenuous physical work during mountain climbing, and it seems reasonable to assume that at those times the upper two-thirds of the left lung was not replaced by pulmonary cysts. It is believed that while the pulmonary cysts resulted from a congenital abnormality of the bronchial tree, their actual formation was not until adult life. The most striking feature of this case is that over a period of approximately ten years there has been no significant change in the pulmonary condition.

C. L.[3]: White male, aged 40 years, a musician, was admitted to hospital in 1931. He gave a history of having had pneumonia without complications at age of five years, malaria at ten years of age and influenza in 1915. He states he has noted some slight shortness of breath for ten years, and had some slight cough at intervals during the past eight years.

In June, 1931, he had an acute respiratory infection and was admitted to the hospital. A routine X-ray revealed a condition of the left lung which was diagnosed as spontaneous pneumothorax. He was admitted to Fitzsimons Hospital in August, 1931, and gave as his complaint "mild dyspnoea with slight unproductive cough."

Physical examination was essentially negative except for the left hemithorax which presented the physical signs of a pneumothorax.

[3] This case has been reported previously in *The American Review of Tuberculosis, 1933, xxvii, no. 1.*

X-Ray: The X-ray film of the chest presented marked rarefication of the upper one-half of the left hemithorax. The upper third of the left lung field appeared to be entirely devoid of any structure. The lower border of this area consisted of a fine but dense line of a long sweeping character. This line extended from the sternal border at the level of the 2nd intercostal space to the periphery, fading out at the level of the 3rd rib anteriorly. Just below this line was another of similar character which also bordered a rarefied area, but the latter area contained delicate lung markings. The lines described as borders of clear areas of the lung were of a long curved character, and presented no apparent pleural attachments. The lower half of the left lung field showed slight increase in density, with exaggeration of the normal lung markings along the basal bronchial trunks. The diameters of the two hemithoraces were approximately the same. The mediastinum was pushed slightly to the right. The right lung showed a slight increase in fibrosis of the upper lobe.

Bronchoscopy: Bronchoscopic examination performed for the purpose of bronchography resulted in failure to locate the main bronchus to the upper lobe of the left lung. Instillation of lipiodol failed to visualize this bronchus.

Artificial-Pneumothorax Induction: The upper third of the left hemithorax was so totally devoid of visible structures that an artificial pneumothorax was induced to visualize the lateral border of the upper cysts. This was accomplished, and the lateral cyst-wall was properly visualized.

Discussion: This case presented one of differential diagnosis. The pulmonary cysts were multiple in character; but the larger one above presented no visible structures and in the X-ray film resembled a partial spontaneous pneumothorax. By consideration of certain characteristic lines in the X-ray film it was concluded that the condition was one of pulmonary cystic disease. This was confirmed by the induction of artificial pneumothorax as a diagnostic procedure.

G. C.: White; male; aged 37 years; farmer; admitted to Fitzsimons Hospital January 12, 1934. His complaint upon admission was dyspnoea and discomfort in the left hemithorax. He gave a history of progressive dyspnoea over a period of years. He had had attacks of chronic cough with copious sputum since 1926. He had worked on a farm, and during the last few years experienced dyspnoea and fatigue following moderate physical exertion. Prior to 1926 he was capable of performing very strenuous manual labor. Was in the military service during the world war.

Physical Examination: General physical examination was negative except that of the chest. In the right lung were numerous sibilant râles, anteriorly and posteriorly. The left hemithorax showed diminished expansion, hyper-

resonance, absence of breath-sounds, decreased vocal resonance, decreased fremitus and plus coin sound.

X-Ray: The X-ray film presented a very marked rarefication of the entire right hemithorax except for an area in the medial third of the lower hemithorax. In the rarefied areas no characteristic lung markings were visible except those of the great vessels. There were seen traversing these areas a few very delicate linear markings as are seen in cases of pulmonary cystic disease. The left lung presented an increase in lung density. This density was especially noted in the region corresponding to the distribution of the bronchi and the pulmonary vessels. The right hemithorax was 2.5 cm. greater in diameter than that of the left.

Bronchoscopy: Bronchoscopic examination revealed very small bronchi supplying the upper and middle lobes of the right lung. These bronchial trunks were too small to permit satisfactory examination. Purulent secretion was noted in the bronchi of the left lung.

Bronchography: Bronchoscopic instillation of iodized oil into the bronchi of the right and left lung presented by X-ray film a normal-sized bronchial tree on the left. The right bronchial tree, however, appeared to be infantile in type. The bronchi to the upper and middle lobes were very small and short. These small short bronchial trunks terminated rather abruptly in tiny ramifications. The main bronchus to the lower lobe, while somewhat shortened and presenting small branches, was about normal in calibre. In the rarefied areas of the right lung no bronchial markings were visualized toward the lung periphery.

Discussion: This patient apparently was a normal healthy individual, capable of performing strenuous physical work prior to 1926. Since then, through a gradual increase in dyspnoea and fatigue, he is now capable of performing only light work. It would seem from the clinical history that he had acquired a condition of the right lung which had caused his disability. The disability was of a very gradual, progressive character, consisting of cystic degenerative changes in the right lung. These changes were brought about by a congenital developmental defect of the bronchi of the upper and middle lobes of the right lung. The lower lobe, while sufficiently supplied with bronchi for proper respiratory function, could not function because of compression from dilatation of lung parenchyma of the other lobes of the lung. The copious sputum evidently came from a chronic, purulent bronchitis of the contralateral lung.

Extreme, localized, pulmonary emphysema with large bleb-formation may closely resemble cystic disease of the lung. The physical signs of

the two conditions may be essentially the same. The blebs may be so large that the interpretor of the X-ray film may be somewhat confused as to the true condition. The aetiology of the two conditions is different. In these patients with extreme localized pulmonary emphysema, the aetiology has been one of localized spontaneous pneumothorax in the presence of a preëxisting pulmonary emphysema. The spontaneous rupture of an emphysematous bleb, surgical or accidental puncture of a bleb in the presence of partial pleural symphysis, has resulted in long-continued partial pneumothorax. The long compression of lung tissue with adherent pleura intereferes with reëxpansion, leaving only a small portion of emphysematous tissue to expand and fill the pneumothorax space. This may result in extreme dilatation of emphysematous blebs. One patient presented large dilatations resembling pulmonary cysts following a spontaneous pneumothorax over the lung base. This occurred in a patient with moderate upper-lobe caseofibrous tuberculosis bilaterally with compensatory emphysema at the bases. Extreme dilatation of emphysematous lung tissue resulted in cyst-like structures. Another patient with pulmonary emphysema of the lower lobe was stabbed with a knife and developed a valve-type spontaneous pneumothorax. When the valve-like opening closed, the already emphysematous lung tissue dilated and filled the small localized pneumothorax area. This area now resembles a pulmonary cyst in that a circular area is observed in the film and this area is apparently devoid of lung structure.

The condition was also observed in another patient who had lobar pneumonia of the lower lobe complicated by a localized pneumococcic empyema. The empyema proved rather chronic, and the long localized pulmonary compression, thickening of the visceral pleura and the accidental introduction of air from time to time resulted in interference with pulmonary reëxpansion. Only a limited portion of lung tissue was capable of reëxpansion to refill the space and this resulted in marked dilatation of air cells of the particular area. The hemithorax now presents a localized circular area with sufficient rarefication to resemble a cyst. Localized dilatation of pulmonary emphysematous blebs may resemble pulmonary cysts which result from embryonic developmental defects. Detailed study as to the aetiological factor or factors responsible for the pulmonary changes should enable the observer to differentiate the two pulmonary conditions.

N. B.: White; male; aged 45 years; farmer; admitted to hospital in December, 1929. He gave the history of having had pulmonary tuberculosis for a period of years. He had, however, improved and had again resumed work. In November, 1929, he was seized with a sudden, sharp, stabbing pain in the lower hemithorax. Upon admission to hospital in December the X-ray film revealed what appeared to be a localized spontaneous pneumothorax. Exploration with a pneumothorax needle showed the intrapleural pressure of this area to be positive plus 2, plus 4. The removal of 400 cc. of air caused a reduction of this pressure (0–1), with comfort to the patient. The heart, which was pushed to the right, returned to a more normal position. The pulse-rate, which was 120, decreased to 84 per minute. The diaphragm, which was somewhat flattened, elevated to its dome-shaped position. After removal of air the symptoms of cardiac embarrassment and chest pain did not return, and the patient elected to leave the hospital. He returned in November, 1933, and the X-ray showed findings identical with those observed in 1929. The size of the rarefied area had not changed. The linear markings, especially the fine, dense, curved ones traversing or bordering the apparent space, were unchanged.

X-ray Interpretation. X-ray of the chest presented in the lower left hemithorax an area of rarefication measuring 5.5 x 4.5 cm. in diameter. The lower border of the area was formed by the left diaphragmatic leaf, while the upper border was formed by multiple, slightly curved, fine, dense lines. Just lateral to this was a similar area, though smaller. The borders of the latter rarefied area were, likewise, formed by fine, dense, curved lines. Several fine linear markings traversed these apparent spaces. There was evidence of a healed, nodose, pulmonary tuberculosis in both lungs. There was a heavy dense line, running from the region of the left hilum upward and outward to the first intercostal space. The diameter of the left hemithorax was 2 cm. greater than the right hemithorax.

Discussion: Patient, N. B., doubtless had a localized spontaneous pneumothorax, as the left chest shows certain bizarre markings usually seen following pneumothorax in the presence of partial pleural symphysis. The rarefied area now observed is due to excessive dilatation of air-cells of the lung. This has taken place because most of the lung tissue about the particular area was rather incapable of reëxpansion, because the pleural surfaces became adherent during compression of the lung by spontaneous pneumothorax. The spontaneous pneumothorax occurred long before admission to hospital. When he was admitted here, the marked localized emphysema had been present for some time. The

recent pain and discomfort resulted from the spontaneous rupture of an emphysematous bleb. The X-ray films of this patient illustrate how, under certain conditions, the air-cells of the lung parenchyma may become greatly dilated. This dilatation may be sufficiently extensive to resemble cystic disease of the lung.

H. H.: Colored; male; aged 39 years; first came under observation in 1931. He was observed for pulmonary tuberculosis at that time, but no activity was demonstrable. He presented at that time a moderate pulmonary emphysema at both bases. On May 28, 1932, he incurred a stab wound which penetrated the lung and produced a localized pneumothorax. Because of puncture of an emphysematous bleb the pneumothorax existed for some time. The valve-type opening finally closed, and reëxpansion was accomplished slowly. Only a small portion of lung tissue was capable of reëxpansion and this portion was already emphysematous. The X-ray film now presents an area in the left lower hemithorax which resembles a cystic area.

X-ray: The X-ray film presents a circular rarefied area in the lower left hemithorax. This area extends from the left diaphragmatic leaf to the anterior end of the 6th rib. The area is 3 x 4 cm. in diameter. The border of the circular rarefied area consists of fine dense lines. Traversing the apparent space is another fine dense line of a curving character. The base of the contralateral lung has the appearance of an emphysematous condition. The upper lung fields are apparently normal.

CONCLUSIONS

1. Clinical investigation of our patients with pulmonary cystic disease indicates that the pulmonary cysts have resulted from an embryonic developmental defect of the bronchus or bronchi of the particular lobe or lobes of the involved lung. Other possible aetiological factors are recognized.

2. The clinical histories of these patients seem to indicate that while an aetiological factor of a congenital character was present, the actual cystic formation in the lung may have been acquired later in life. This conclusion seems plausible because of obtaining a definite history of ability to undergo strenuous physical exertion for a period of years without dyspnoea. This was followed by a period of progressive dyspnoea, finally ending in varying degrees of physical disability. These patients vary as to symptoms from that of moderate dyspnoea to one of extensive dyspnoea approximating invalidism.

3. Methods are discussed concerning differential diagnosis, especially

in regard to differentiating pulmonary cystic disease from spontaneous pneumothorax.

4. Spontaneous pneumothorax developing over an area of pulmonary emphysema may result, during pulmonary reëxpansion, in extreme dilatation of emphysematous blebs. These huge blebs may closely resemble cystic disease. They may, however, be differentiated from cystic disease by determination of the aetiological factor which produces the pulmonary changes.

POSTSANATORIUM CARE AT THE BELLEVUE SETTLEMENT HOUSE[1]

CLARA REGINA GROSS[2]

The tuberculous patient on leaving the hospital or sanatorium, where he has spent months in an effort to arrest his disease, faces several very distinct problems—problems which at first seem to be insurmountable. The first is that of changing from a regimen in which rest is the keynote to an environment, where, not rest, but work with its attendant exercise, physical and mental strain, is the dominant note. Family, friends, and employers do not comprehend the need of further rest on the patient's part, particularly if the patient appears rather robust. The patient, himself, after remaining for months on a very rigid regimen, often too frequently arrives at the conclusion that he must not exercise or work for fear of reactivation of his disease. Some go to the other extreme in working without regard for their past training. It is therefore difficult for most patients to make the jump between the regulated hospital or sanatorium environment to one which he, himself, must regulate. Social adjustments are therefore often needed and must be dealt with adequately.

The second problem is that of work. Work must be of a nature as to be within the natural endowments and the physical capabilities of the patients, and at the same time enable the individual to be self-supporting. Of equal importance is the problem of medical supervision.

With the aim of providing an opportunity whereby these adjustments may be accomplished, Dr. James Alexander Miller, Director of the Tuberculosis Service at Bellevue Hospital, New York City, organized the Bellevue Settlement House.

Dr. Miller had already begun the day treatment for tuberculous patients on the old ferry-boat "Southfield," which he had moved up and moored to the front of Bellevue Hospital. This was the beginning of

[1] Presented at a meeting of the Tuberculosis Sanatorium Conference of Metropolitan New York, May 22, 1935, Nassau County Tuberculosis Sanatorium, Farmingdale, New York.

[2] Assistant Visiting Physician, Tuberculosis Service Bellevue Hospital; Physician-in-Charge, Bellevue Settlement House.

the Day Camp Boat in 1908. An open-air public-school class, and speech-defect and posture classes for children were started. Occupational therapy was begun. A day nursery was opened. Arrangements were made for tuberculous patients to sleep on the boat. While the hospital supplied the food and some of the funds, the Auxiliary to the Tuberculosis Service paid the greater part of the upkeep of the boat until 1916 when the City took over the maintenance of it. Its activities grew. By 1910, seventeen men were sleeping on the boat. It soon became evident that a similar arrangement was needed for women. Thus the Bellevue Settlement House came into existence in 1911 at the suggestion of Dr. Miller. The house at 206 East 30th Street, New York City, was obtained and is still being used, and Miss Alice E. Clements has been the director since the beginning. It accommodates 22 patients, part of whom cured on the Day Camp Boat during the day while some were able to keep their jobs and work daily. In 1918 there was a need for a temporary home for contact children. This experiment was continued until 1923, when it was discontinued primarily because of the more pressing need for homes for the adult patients, and later particularly for pneumothorax patients, who no longer needed hospital care but close medical supervision and continued curing.

In 1917 the building at 206 East 30th Street was presented to the Auxiliary by Mr. W. Eugene Kimball, and the house was thereafter to be known as the Edith Gibb Kimball Memorial. The Auxiliary has the entire burden of raising the funds for the Settlement House work. The undertaking is therefore a private one. The City, however, allows the use of the name Bellevue Settlement House and gives all medical care and use of the Day Camp Boat.

In the beginning the patients were selected by the clinic physicians from among those registered in the Tuberculosis Clinic in Bellevue Hospital, qualifications for admissions depending upon the probability of improvement under the additional opportunities, which included careful supervision and the supplying of special needs beyond the patients' means. Now, however, the patients come from numerous sources,—Bellevue Hospital, various municipal and State sanatoria, Stony Wold and Potts Memorial, as well as various private hospitals in New York City, and welfare agencies such as the Association for the Improving of the Condition of the Poor, the Catholic Charities, Charity Organization Society, and the Committee for the Care of the Jewish Tuberculous. Some may come on their own initiative, having heard of the Settlement House

through previous patients. They may be patients who are either awaiting sanatorium care, or preferably those who have had a period of hospital or sanatorium curing and who need to be gradually rehabilitated under more favorable and supervised regimen than they would otherwise have. A summary of the status of those present at the house now shows that ten are working, 3 going to school, and 9 are still curing and attending the Day Camp Boat. Of these 9, six are able to work if work is available.

The actual medical care is under the direction of the Bellevue Tuberculosis Service. The patients have record forms, giving their histories, the detailed record of their symptoms including their general condition, temperature, pulse, weight, cough, expectoration with its character and amount, haemoptysis, gastrointestinal symptoms, etc.; notes of special treatments if any; type and amount of work; and notes of physical examinations. This record is in the possession of the patient and is available at any time for the examining physician or agency or individual interested in the patient. The record the patient fills out each week and brings with her at the time of her examination. Each patient is examined, X-rayed, and has a concentrated sputum examination once a month or more frequently if necessary. If the patient needs treatment for conditions other than pulmonary, she is referred for the proper medical care. Her condition is discussed very frankly, and advice is given accordingly in exact instructions regarding either curing or working. At intervals, particularly in the pneumothorax cases, or if there is any unusual problem about the patient, the latter is presented at our weekly Out Patient Department conference before others of the medical staff of the Tuberculosis Service. Here the patient again hears a great deal of our discussion and receives advice regarding her particular problem. At intervals there have been talks by various members of the medical staff on some phase of tuberculosis, either in a direct educational line or in encouragement to them. This educational process, with our policy of frankness, is often tedious and time-consuming, but one which apparently justifies the result. Patients seem to appreciate it, and often after leaving the Settlement House come back asking for our advice. They seem to develop a greater respect for the disease itself, and for an honest difference of medical opinion which may exist, and for the difficulty in managing certain cases, all eventually helping in the educational process of their learning to live with their disease, not only for the time

they are at the Settlement House, but for the future as well—an education which we feel is a duty to the patients.

The limited number of patients affords an excellent opportunity for close medical and nursing supervision. It is obvious that the nurse in charge must be a capable person, acting as an executive in managing the house, as well as a social service worker with a special training in tuberculosis, and possessing a keen understanding of people, especially patients with their numerous problems and needs. To keep 22 girls happy and directed wisely on their road to rehabilitation obviously takes much energy, skill, enthusiasm and diplomacy. Such a person is found in Miss Alice E. Clements, who has been the nurse in charge since the opening of the Settlement House.

The Settlement House is an "old fashioned" house which has been altered to accommodate 22 patients. A dressing cubicle and clothes closet is provided for each girl. The roof has been converted into a sleeping porch with sliding windows on three sides, which except in driving rain or snow are wide open, affording splendid circulation. Proper outdoor sleeping clothing is provided. A well-balanced high caloric diet, including a quart or more of milk and a liberal allowance of eggs, with sufficient variety to suit various tastes, is provided. A large assembly room with a piano, victrola, radio, and books makes a pleasant place for the evening. Frequent entertainments are given, or patients may receive guests in the evening. It has been the constant aim to make a real home for the patients and to avoid institutionalism as much as possible.

A nominal charge of $7.00 per week for each patient is made. There are, however, 4 free beds, maintained by the Auxiliary to the Tuberculosis Service, which carries the burden of maintaining the house. Inability to pay, therefore, never bars a patient. Either through the assistance of the Auxiliary or kind friends, or various means, the fee is met in part or whole. At the present time, of course, these agencies are taxed to the limit, because of the ever-increasing cry for free beds. The latter request is usually from the pneumothorax patient who has had an extended period of hospital or sanatorium care and whose home conditions are unsatisfactory and yet who needs continued medical care and a protected environment, or from the patient who needs to be rehabilitated.

Reference to the following chart will show the number of paid and free patients:

All patients discharged between 1911–1935

Self- and part-payment	219	(9 per year)
Organizations and individuals	108	(4 per year)
Free patients	480	(20 per year)
Total	807	(33 per year)

Among patients discharged between 1911–1930

Self- and part-payment patients	174	(9 per year)
Paid for by organizations or individuals	55	(3 per year)
Free patients	408	(21 per year)
Total	637	(33 per year)

Among patients discharged between 1930–1935

Self- and part-payment patients	45	(9 per year)
Paid for by organizations and individuals	53	(10 per year)
Free patients	72	(14 per year)
Total discharged	170	(34 per year)

These figures show two interesting facts: First: That the ratio of self- and part-paying patients remained about the same before and during the "depression." Second: That while the number of free patients has decreased, the number paid for by organizations such as the Association for the Improving of the Condition of the Poor, the Catholic Charities, Charity Organization Society, the Haven's Fund, the Committee for the Care of the Jewish Tuberculous, or individuals, has correspondingly increased. These facts are certainly very gratifying, especially at a time when agencies or individual funds are at a low ebb. We, therefore, regard it as a real appreciation of the need of an institution like the Settlement House, and as direct approval of our program and confidence in our work.

Since the inception of the work 807 patients have been cared for at the Bellevue Settlement—an average of 33 per year. Grouped according to their diagnosis on admission they are as follows:

Tuberculous

		Approximate per cent
Pulmonary, first stage	267	33
Pulmonary, second stage	232	29
Pulmonary, third stage	79	10
Pulmonary, pneumothorax	82	10
Nonpulmonary, joint, lymph nodes, etc.	67	8

Nontuberculous		
Observation	22	3
Contact (the infants cared for 1919–1923)	58	7
Total	807	

Length of stay among patients discharged between 1911–1935

		Approximate per cent
Over 1 month and less than 3 months	331	41
Over 3 months and less than 6 months	204	25
Over 6 months and less than 9 months	100	12
Over 9 months and less than 1 year	72	9
Over 1 year	100	12
Total discharged	807	

Record of patients discharged 1911–1935

Alive	540	67
Dead	101	13
Untraced	166	20
Total	807	

These figures are interesting, since about 80 per cent of the patients for a 25-year period—from 1911–1935—are accounted for, and 20 per cent untraced. It might be well to note that all the social-service work at Bellevue Settlement House was done by the director in addition to her duties in the detailed management of the house, and that it includes all clerical work and bookkeeping.

When the patient first comes to us she has a very careful social diagnosis made by the director, Miss Clements. This in certain cases may be supplemented by psychiatric consultations. Those who are awaiting sanatorium care are studied, as well as those who expect to return to work. This interview, followed by as many as are needed, is particularly helpful to the patient in her mental and physical readjustment from the hospital or sanatorium to her new environment. Each patient is then seen by the physician in charge, who after a physical examination, X-ray and a concentrated sputum, establishes the physical status of the individual and outlines the exercise or type of activity in which the individual may engage. When the patient has been given a favorable prognosis, the next problem, that of work, either the old job or a new one, is studied. After an analysis of the educational background, social status, vocational desires, aptitude and skill of the patient, is made, a plan is outlined for her rehabilitation as a self-support-

ing or future self-supporting individual. In doing this we have called upon every type of agency existing in New York,—hospitals, industrial concerns, sanatoria, welfare groups and the State Rehabilitation Bureau,—all of which affords unusual opportunity for the possible rehabilitation plans of the patients.

The patients varied in their intelligence, background, and education. Most of them returned to their previous occupations. It would be interesting to note how many of these suffered any alteration in their income as a direct result of their previous illness, and, if so, how long. Unfortunately, we do not have such information available. But the fact remains that many of the patients returned to their former occupations. Some, however, could not, either because of their physical status, or because of the unfavorable working conditions, or because of an inability to make the necessary mental and physical adjustment after curing.

The following tables represent the present status of the patients. We have divided the patients into two groups, those of 1911–1930 and of 1930–1935. Since 1930 there was a definite increase in the number of pneumothorax patients; hence a definite change in the patients' regimen and medical care. Coincident with this change, came a definite difference in the type of patient entering the Settlement House. The newer patients are of a finer calibre than previously. They are more intelligent and with a little better educational background and therefore more coöperative in effecting the arrest of their disease and in becoming rehabilitated.

Physical status on discharge	*1911–1930*	*1930–1935*
Stage I	217	50
Stage II	201	31
Stage III	62	17
Pneumothorax	21	61
Joints and lymph nodes	59	8
Observation	19	3
Contact (including infant group 1919–1923)	58	0
Total	637	170
Present status		
Working	286	79
Married and caring for home	85	51
In sanatorium or hospital	15	24

	1911-30	1930-35
Dead	91	10
Untraced	160	6
Total	637	170

The vocations to which the patients in the second five-year group have returned are varied. The following represents the present occupations:

Present occupations of working group: 1930–1935

Secretarial	17	X-ray	1
Clerical	13	Milliner	1
Artist	2	Sales clerk	5
Teacher	1	Social-service aid	1
Public-health nurse	1	Library worker	1
Trained nurse	1	At school	12
Telephone operator	2	Married and caring for home	51
Factory worker	9	Household help	10
Matron	1	Dietitian	1
		Total	130

The problem of work is a very serious one confronting the patient on leaving the sanatorium. Work must be of such a nature as to be within the scope of her natural endowments and at the same time to enable her to be self-supporting, and, again, work which will be within her physical capabilities. There are several possibilities in solving this problem. The patient may return to her old job, as we have mentioned previously. Sometimes, however, this cannot be done. Either the employer refuses to reinstate the patient in her old job, or the old job for various reasons is quite unsuited to the physical and mental condition of the patient. Unless changes in the old job can be made, the patient would be running considerable risk. Sometimes employers are quite willing to adjust working conditions to the impaired working capacity of the tuberculous individual, and happy is the patient who is so fortunate. To-day, however, with economic conditions as they are, employers are less willing to make exceptions and it becomes increasingly difficult for the handicapped to find modified working conditions to suit her capacity. If a patient cannot regain her old job, then it becomes necessary to train herself for some new work. Indeed, in the past 5 years it has become very striking to see how ambitious the patients have become and how they have definitely desired to change the whole plan of their life with a new vocation.

During 1930–1935, reëducational work was made possible, as is shown by the following table:

Reëducational work for 5 years: between 1930–1935

Typist	4	College	1
Secretary	16	Technician, X-ray, bacteriology, at hospitals	2
X-ray and bacteriological	1	Training school for nurses	3
Addressograph and office machines	2	Scientific housekeeping	2
Trade schools	4	Sheltered work shops	5
High schools	6		
		Total	46

This table is not only evidence of what can be done for individual patients, but an indication of the possibility to secure employment for the tuberculous even in a very poor labor market.

Since tuberculosis is a relapsing disease, the patient always lives with the constant possibility of a relapse. The relapses of most patients occur within two years following sanatorium care. Competent and continued medical supervision is therefore necessary, especially so during the period immediately following discharge from the sanatorium. This is particularly true if the patient has appreciated the significance of the treatment in the sanatorium or hospital. Symptoms of a subjective nature do not constitute a sufficient guide to advise her what to do. In the sanatorium the doctor managed everything. Industry may have its medical service, but in few is it individualized to the extent where the patient's personal needs and problems are cared for adequately.

Looking at these problems from the point of view of society, we find that it looks upon her as an individual in whom it has invested a certain amount of money in order to secure an arrest of the disease. Is the patient in response going to be able to return to a productive life and pay back what has been invested on her? Public health workers are asking also where the responsibility for providing employment exactly rests, and if conscious attempts to provide a protected environment or sheltered employment really help materially to reduce the relapse rate of the disease.

Various attempts to provide sheltered employment have been tried in this country and abroad. Notable examples are Papworth Village in England, and in the United States the Altro Shop, the Olive View

Convalescent Camp, Potts Memorial, the Reco Shop, and the Minneapolis Program.

By and large, most of these programs have been designed primarily for industrial convalescence and for the hardening up of the patient, an intermediary stage of treatment in tuberculosis, and are, therefore, a part of the physical restoration of the individual. These projects have been very wholesome and commendable ones, attempting to train the individual for some trade, and reëstablishing her as an economic asset. There has been one main objection, however, to them. Each has usually begun with some form of solution and tried to fit the individual patients into that solution. In other words, each emphasizes the activity and seeks to adapt the individual patient into that activity. The number of possible occupations offered is, therefore, relatively small, and the actual number of jobs small. By these statements I do not mean to minimize the immense contributions these various efforts have made towards the problem of rehabilitation.

To place the program of rehabilitation on a surer footing, however, it certainly seems wiser to begin with the individual patient, and the recognition of her problems. An analysis of her educational background, social status, vocational desires, aptitude, skill and physical capabilities should determine the type of work which can best make the individual self-supporting. Social adjustments in changing from the regimen of curing to that of work must be recognized and dealt with accordingly. Close and individualized medical supervision caring for the patient's personal needs must be provided. On the basis, therefore, of a complete picture of the patient, with her physical and social problems, attempts should be made to rehabilitate her according to her individual needs. That such rehabilitation of the tuberculous patient is possible of achievement, has been demonstrated over a period of 25 years at the Bellevue Settlement House.

COMPARATIVE TUBERCULOSIS FINDINGS AMONG INDIANS AND WHITE PERSONS IN CATTARAUGUS COUNTY, NEW YORK[1,2]

JOHN H. KORNS

An investigation of the amount of tuberculosis among Reservation Indians in Cattaraugus County, New York, has seemed desirable since the tuberculosis death-rate recently in this group had been about six times that of the white population within the County. For the entire seven years ending December 31, 1934, 15 tuberculosis deaths were recorded among the 972[3] Indians in the above reservation, giving an average annual rate of 220.4, while the deaths among the 72,527[3] white population numbered 183, an annual rate of 37.3. The average age at death of the Indians during this period was 28.7 years, and of the whites 38.7 years. Throughout the study it was thought that unreported active cases of tuberculosis might be discovered and placed under treatment. Since figures showing the incidence of tuberculous infection and disease among white persons in the County have been made available through combined studies by the County Department of Health, the Milbank Memorial Fund, and the United States Public Health Service, it was thought that useful epidemiological data regarding tuberculosis might be secured by comparing the findings in the two racial groups.

Other studies among Indians reported in recent years all tend to show a high incidence of tuberculous infection and a high death-rate from the disease. Crouch (1) found 75 per cent of full-blood Indian school-children in Montana reacting positively to 0.1 mgm. O. T., whereas 22.6 per cent of white school-children reacted. Burns (2) tested 2,125 Minnesota Indians of all ages and found 37.8 per cent positive before age 5, with an increasing incidence up to 83.9 per cent in the 20–24-year age-group, the incidence then remaining about the same during

[1] From the Cattaraugus County Department of Health. Acknowledgments are made to the Milbank Memorial Fund for permission to use unpublished data and to Miss Jean Downes for help in tabulating these data and for helpful suggestions.

[2] Published with the permission of the Office of Indian Affairs.

[3] Average annual population during the years 1928–1934 inclusive, based on the United States Census of 1920 and 1930.

the older age periods. Aronson (3) reported on tuberculin tests among rural white and Indian school-children in Michigan with results as follows: 5–9-years white children, 9.6 per cent positive; Indians, 25 per cent positive: 10–14-years white children, 17.8 per cent positive; Indians, 69.7 per cent positive: 15–19-years white children, 26.4 per cent positive; Indians, 69.3 per cent positive.

Some information is at hand also as to the amount of tuberculosis demonstrable by X-ray among the Indians surveyed. Burns (2) X-rayed 1,163 positive reactors of all ages and found an astonishingly large amount of tuberculosis. Of this number 645 showed calcified tracheobronchial lymph nodes, calcified primary nodes, pleural adhesions or parenchymal infiltration. Only 609 films were considered negative. Montgomery (4) X-rayed 147 Indian students in Manitoba, and found 3.4 per cent to have active pulmonary lesions, 6.8 per cent latent pulmonary lesions and 50 per cent latent foci of tuberculous infection. Montgomery took oblique as well as posteroanterior films, thus adding to the accuracy of his diagnoses.

As to tuberculosis deaths among Indians, figures for the year ending March 31, 1934, including all Indians in the United States, except the Five Civilized Tribes and certain agencies not reporting, showed a tuberculosis death-rate of 250 (5). The rate for 1925 was apparently 630 (6). Crouch (1) found in six reservations in Montana that the full-blood Indians showed a tuberculosis death-rate of 1327.4; those of one-fourth and more Indian mixed blood a rate of 339.1; and those of mixed blood less than one-fourth Indian a rate of 52.3. The tuberculosis death-rate for the Indians as a whole was 787. Ferguson (7) reported that in 1931 among 122,911 Canadian Indians the tuberculosis death-rate was 546.7, or 7.5 times the rate of 73.6 for the total population of Canada. Since the general death-rate among Indians for the same year was less than twice that of the entire population, the relative seriousness of tuberculosis as compared with other causes of death is apparent.

These surveys agree in finding an extremely high death-rate from tuberculosis among the Indians. Those studies dealing with infection have shown an earlier and higher rise in the infection incidence than among white persons in the same areas.

ALLEGANY RESERVATION INDIANS

The 972 Allegany Reservation Indians live on a strip of land 40 miles long, bisected throughout its length by the Alleghany River. From

each bank the Reservation extends approximately a half-mile, and the land is arable and fertile. There are about 24 Indians per square mile, while there are about 32 white persons per square mile in the rural and village sections of the County. The Reservation Indians consist of half-breeds or those with less than half Indian blood. They are enrolled according to the old custom of following the lineage of the mother; so there are no records in the Indian office by which the proportion of Indian blood may be determined. About 84 per cent are Senecas, the remainder being chiefly Onondagas and Tuscaroras. They live largely in two-room houses, with a minimum of sanitary provisions, on diets often deficient in vitamins and with a superabundance of carbohydrates. A certain amount of public money is available for their more urgent medical needs. They accept medical care rather freely, as is evidenced by the fact that 63 had had tonsillectomies, 18 appendicectomies and 26 additional Indians had had other major operations. Twelve had had sanatorium care for tuberculosis. Following the completion of this survey 26 additional persons submitted to tonsillectomy and 54 others came under medical care. At present, 22 are receiving antisyphilitic treatment.

The Reservation Indians mingle with the white population outside of the Reservation in high-school, at movies, and in domestic or other work. A considerable number of white persons live within the area of the Reservation.

METHODS OF THE SURVEY

Through the financial coöperation of the Indian Bureau at Washington the County Department of Health arranged for a series of clinics within the Reservation. A T.E.R.A. nurse was assigned to the work of visiting homes and setting up clinics. This nurse made no mention of tuberculosis to those she invited to the clinic, but stressed its health-examination feature, and held out the hope that important health needs might be met through public funds. Later, these were actually provided for in part through the County Department of Public Welfare and the State Division of Social Welfare. The clinician of the Bureau of Tuberculosis made the examinations consisting of a partial physical, an X-ray of the chest and a tuberculin test. In many instances blood, sputum and urine specimens were taken and were examined in the County Department of Health Laboratory. The tuberculin used was standardized by the New York State Department of Health and was as potent as

that used in the series of tests among white persons to be mentioned later in this paper. In nearly all instances only one test of 0.1 mgm. O. T. was given. This was read after 48 hours, the Henry Phipps technique being observed.

TABLE 1

Results of tuberculin tests on Indians according to age and sex

AGE	PER CENT POSITIVE	NUMBER POSITIVE	NUMBER TESTED
		Male	
All ages	44.6	126	282
0–4	5.1	2	39
5–9	31.0	18	58
10–14	30.0	15	50
15–19	46.4	13	28
20–24	50.0	8	16
25–29	56.2	9	16
30–34	63.6	7	11
35–39	90.0	9	10
40–49	76.1	16	21
50–59	83.3	15	18
60 and over	93.3	14	15
		Female	
All ages	48.0	161	335
0–4	8.5	4	47
5–9	20.9	9	43
10–14	33.9	20	59
15–19	46.1	12	26
20–24	54.8	17	31
25–29	59.2	16	27
30–34	72.4	21	29
35–39	85.7	12	14
40–49	90.4	19	21
50–59	80.7	17	21
60 and over	77.7	14	18

SURVEY DATA

Thirty-two clinics were held between October, 1934, and June, 1935, in which 650 were examined. Of these, 298 were males and 352 females. The number examined constitutes two-thirds of the Indian population of the Reservation. Some of the remaining third were away attending

school, accounting for the smaller number examined in the 15–19-year group; some were working outside the Reservation. In so far as the Health Department records may be used as a criterion there is reason to believe that the 650 examined are representative from a health standpoint of the Reservation as a whole, except for 3 hospitalized cases to be mentioned later.

Six hundred and seventeen were tuberculin tested. The incidence of positive tuberculin reactions (table 1) was 44.6 per cent among 282

TABLE 2

Types of tuberculous lesions found in Indians X-rayed according to age-groups

TYPE	ALL AGES	0–9	10–19	20–29	30–39	40–49	50–59	60+
Total lesions	89	8	19	12	14	6	18	12
Reinfection types:								
Pulmonary:								
Minimal	14		1	3	1	1	5	3
Moderately advanced	3				1	1	1	
Nonpulmonary	8		1	2	1		3	1
Childhood (primary) type:								
Calcified nodules in lung	12	1	2	3	2	2	2	
Tuberculosis of tracheobronchial lymph nodes:								
Calcified	25	2	8	2	5	1	3	4
Caseous	1	1						
Both calcified nodules in lung and calcified tracheobronchial lymph nodes	26	4	7	2	4	1	4	4
Total Indians X-rayed	625	171	178	93	70	43	38	32

males and 48.0 per cent among 335 females. It rises early and rapidly and remains high in both sexes.

Interestingly enough, no new definitely active cases of tuberculosis were found among the 625 X-rayed. Table 2 shows 17 cases of pulmonary tuberculosis diagnosed, but the one definitely active case in this group had been known to the Bureau. Possibly one other was active but there was no opportunity to secure further examinations or study of symptoms. In the other 15, repeated examinations and symptom-studies satisfactorily ruled out current activity of the lesions. The total number of diagnoses of tuberculosis of all forms, including primary and reinfection types, pulmonary and nonpulmonary, was 89, or 13.6 per

cent, of the 650 examined. All of the lesions of the so-called childhood type, with the exception of those in a child of nine years, had calcified well. There was evidence of multiple primary infection in several, and of unusually heavy infection in some. Among the 625 X-rayed, therefore, there were at most three who were thought to show active tuberculous lesions, a case incidence of 4.8 per 1,000.

Three other active cases in the Reservation were known to the Bureau but were not examined in the survey since they were already in sana-

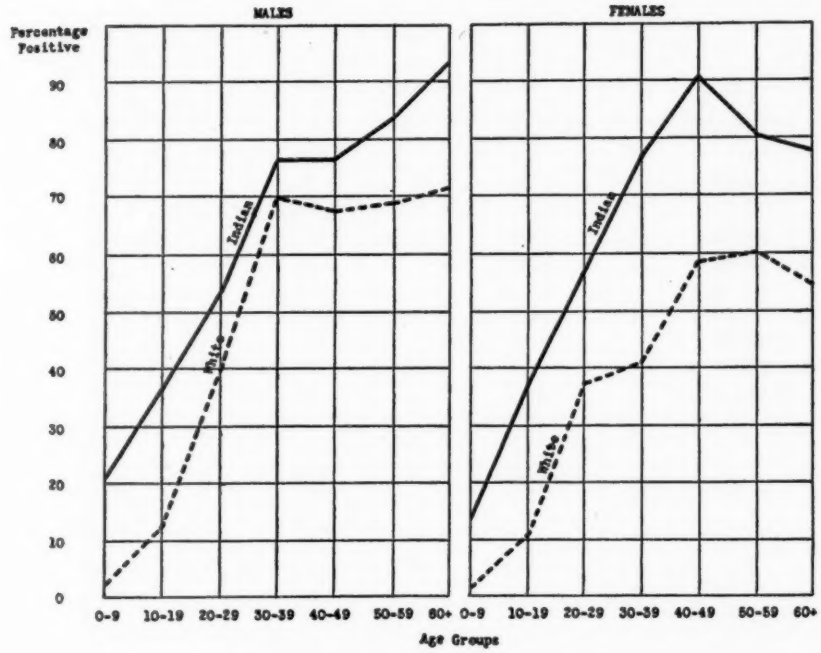

CHART 1

toria. These were all advanced pulmonary cases aged 24, 24 and 19. The entire number of active and questionably active cases of all types now known to the Bureau is, therefore, six. This means an active case-rate of 6.1 per 1,000 in the Reservation of 972 Indians.

COMPARISON OF INDIANS WITH WHITE POPULATION

The tuberculin-testing and X-raying of a random sample of the white rural and village population of the County has been reported in part by

Sydenstricker and Downes (8) and by Korns (9). Subsequent tuberculin-testing increased the total individuals tested to 502 males and 600 females, with results shown in table 3. The total of 1,102 persons represents 21.3 per cent of the population in the geographical area studied, and the various age-groups are rather evenly distributed as table 4

TABLE 3

Results of tuberculin tests on white persons according to age and sex

AGE	PER CENT POSITIVE	NUMBER POSITIVE	NUMBER TESTED
	Male		
All ages	38.6	194	502
0–4	2.0	1	51
5–9	4.7	3	64
10–14	7.1	5	70
15–19	25.0	10	40
20–24	31.0	9	29
25–29	48.0	13	27
30–34	57.7	15	26
35–39	81.5	22	27
40–49	67.7	44	65
50–59	68.8	33	48
60 and over	70.9	39	55
	Female		
All ages	31.7	190	600
0–4	1.7	1	59
5–9	1.4	1	73
10–14	9.1	6	66
15–19	13.2	7	53
20–24	42.5	17	40
25–29	32.6	14	43
30–34	36.4	12	33
35–39	45.2	14	31
40–49	59.1	52	88
50–59	60.3	38	63
60 and over	54.9	28	51

shows. In these tests 1.0 mgm. of O. T. was always given in case a smaller dose caused no reaction. Table 3, by comparison with table 1, shows a higher prevalence of infection among the Indians of both sexes throughout life. The difference is greater among females than among males. Chart 1 illustrates these points graphically. The Indians are

sensitized by the tubercle bacillus earlier and remain in late life more sensitive than do white persons. The discrepancy in these tables would be more marked if the Indian nonreactors had been given 1.0 mgm. In table 4 the Indian infection-rate is adjusted to the random sample group of the white population, so as to eliminate differences in the rate which might be due to inequalities in the age distribution of the two groups. It is seen that, if the Indians tested had had the same age distribution as the white persons, the expected rate among the Indians would have been 55.4, while the rate for white persons, both sexes, was 34.8.

TABLE 4

A comparison of the tuberculous infection-rate among white persons and Indians

AGE-GROUPS	INFECTION RATE		ADJUSTED INFECTION RATE AMONG INDIANS*
	Among White Persons Tested	Among Indians Tested	
All ages	34.8	46.5	55.4
0–4	1.8	7.0	
5–9	2.9	26.7	
10–14	8.1	32.1	
15–19	18.3	46.3	
20–29	38.1	55.6	
30–39	53.8	76.6	
40–49	62.7	83.3	
50–59	64.0	82.1	
60+	63.2	84.8	

* Rate adjusted to the age distribution of the tuberculin-tested white population.

The results as to degree of reaction between white persons and Indians are not strictly comparable, for the reason that the Indians were routinely given 0.1 mgm. O. T. while the white group were given graded doses. At first the routine for white persons was 0.01 mgm.; then a second dose of 1.0 mgm. if negative at first. Later in a good many instances the dose was started with 0.1 mgm. However, some idea of the degree of sensitiveness may be gathered from the fact that, among the 165 white persons reacting to 0.1 mgm., 40 per cent showed a 3+ or 4+ reaction, while, among 251 Indian reactors whose reaction was measured, 50 per cent showed a 3+ or a 4+ reaction. Among 59 white persons diagnosed by X-ray as having tuberculous lesions, 24 per cent failed to respond to 1.0 mgm. of O. T., while among the 89 Indians

diagnosed as tuberculous only 7 per cent failed to respond to 0.1 mgm. These findings would suggest that the Indians under consideration are subjected to repeated infections which maintain tissue hypersensitiveness to tuberculin, while among the white population this is true only to a very limited extent.

As to diagnoses, among the 625 Indians X-rayed, 89, or 14.2 per cent, showed evidence of tuberculous lesions, while among 846 white persons X-rayed only 59, or 6.9 per cent, as shown in table 5, gave this evidence. Neither table 2 nor table 5 shows the same individual twice, even though

TABLE 5

Types of tuberculous lesions found in white persons X-rayed according to age-groups

TYPE OF LESION	ALL AGES	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70+	AGE UNKNOWN
Total lesions	59	1	6	8	6	18	11	5	5	
Adult Type (pulmonary):										
Minimal	7					3	3		1	
Moderately advanced	1						1			
Advanced	1		1							
Childhood Type:										
Calcified nodules in the lung	15		1	2	2	4	3	3		
Tuberculosis of the tracheobronchial lymph nodes calcified	11	1	1	1		4	2	1	1	
Both calcified nodules in the lung and calcified tracheobronchial lymph nodes	24		3	5*	4	7*	2	1	2	
Total individuals X-rayed	846	191	185	93	97	114	84	52	29	1

* In one case the films indicated only partial calcification at the hilum.

tuberculous lesions were found in more than one region. In table 5 no nonpulmonary lesions are listed, since in those few individuals having such lesions pulmonary tuberculosis also was found, whereas in table 2 no pulmonary tuberculosis was discovered in the 8 persons showing nonpulmonary lesions. Of the 89 Indians diagnosed as tuberculous, 17 showed pulmonary, reinfection type lesions, one of which was definitely active and another questionably active. One child showed a primary-type lesion that may have been active, since calcification had not occurred and there was fever. Of the 59 white persons diagnosed as tuberculous, 9 showed pulmonary lesions of the reinfection type, one of which

was active. The ratio of active and questionably active cases among Indians to that among white persons X-rayed was 4 to 1. If, however, the results of the surveys among both groups be added to the known active cases on file with the Bureau of Tuberculosis it is found that the active case-rate for the 972 Indians in the Allegany Reservation is at present 6.1 per 1,000, while that for the 40,000 rural and village white population in the County is 1.3 per 1,000. In view of 12 years of intensive case-finding work by the Bureau of Tuberculosis and very satisfactory reporting of cases by physicians, it is felt that nearly all active cases are known. The ratio of Indian cases to white cases therefore appears to be about 5 to 1, while the ratio of Indian tuberculosis deaths to white deaths is 6 to 1.

The writer had the opportunity of studying all the X-ray films both of the Indians and the white persons, and was interested to note that the Indians showed very good resistance to tuberculosis. There was evidence of extensive calcification of primary foci and of healing by fibrosis and calcification of the reinfection types of lesions. Clinically there was evidence of a healthy condition in the presence of these obsolete lesions.

SUMMARY

The results of a tuberculin and X-ray survey of the Allegany Reservation Indians are presented and compared with the results of a similar survey of a random sample of a rural and village section of the white population in Cattaraugus County, New York. The Indians show a decidedly higher tuberculosis infection, morbidity and mortality rate than do the white persons. The Indians develop sensitiveness to tuberculin earlier in life, show a higher degree of sensitiveness and a more definite persistence of this sensitiveness into old age. It is felt that the Indian active case-rate, which appears to be five times that among the white population, goes far toward explaining these findings.

These Indians show a rather surprising amount of tissue resistance to tuberculosis as judged by their X-ray films. Their resistance appears to compare favorably with that of the white persons under consideration. Possibly the large admixture of white blood in these Indians and their exposure as a group for many generations to tuberculosis account for this relatively high resistance. However that may be, the fact that a fair degree of resistance is present encourages the health-worker who hopes through environment to reduce the tuberculosis death-rate.

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OLEOTHORAX IN COLLAPSE THERAPY OF PULMONARY TUBERCULOSIS

An Experimental and Clinical Study with a Review of the Literature[1]

MINAS JOANNIDES

INTRODUCTION

In our fight to control tuberculosis everyone is anxious to use all available means to check the progress of the disease. From a public-health viewpoint every case converted from an open into a closed case will aid in preventing infection in a variable number of others who are dear and near to the patient. Those with lower resistance, if unprotected, may develop tuberculosis and succumb to it. Until such time, and we hope it is in the near future, as we can successfully produce a lasting immunity against the tubercle bacillus, we should utilize collapse therapy of some form or other because, at least at present, it offers the greatest hope for controlling the disease.

Eleothorax represents a special form of collapse therapy. In those cases in which it is indicated it offers a satisfactory form of collapse. May we ask then with Dufault (3) of Rutland, Massachusetts, that

> granted its application may be limited to a few well chosen cases, granted also that its results may often be but palliative in nature, should it not yet be assigned a place among our other means of collapse therapy? In the phthisiologist's armory all the weapons are not of equal value, nor each as frequently used as another; and, in the war we are waging, can any single weapon be safely discarded?

It is with this in mind that we undertake to present various phases of this mode of therapy, not just to add another paper to the large collection on collapse therapy, but to evaluate various phases of eleothorax.

At this point it may be appropriate to take up the question of terminology in this mode of treatment. It is unfortunate that when Bernou coined the word *oleothorax* he selected a hybrid Latino-Greek word. It is

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also a fact that in chest-work most of the words used are purely Greek in origin. Such words as *thorax, pleura, pneumonia, hydrothorax, pneumothorax,* and *pyothorax* are in common use. Following the same custom may we suggest that the term *eleothorax* be adopted? Such a word would sound better to the ear of the etymologist and would be just as easy to pronounce and remember. This term is already accepted by Thomas Lathrop Stedman, the medical lexicographer, with the following note: "eleothorax (Gk. elaion, oil plus thorax) the injection of oil into a pleural cavity in order to compress a tuberculous lung." In this report, therefore, we will employ this term in the hope that it will be generally accepted.

HISTORICAL

Eleotherapy has been used from time immemorial. The healing qualities of oil were recognized by the evangelist Luke (1), who in his story of the good Samaritan stated that "a certain Samaritan, as he journeyed came where he was [referring to an injured man]; and when he saw him, he was moved with compassion, and came to him, and bound his wounds, pouring on them oil and wine." It is evident then that at the time of Christ the therapeutic use of oil was in vogue as reported by this Evangelist, who himself was a physician. Even before the time of Christ, Hippocrates (2) makes repeated references to the use of oils for therapeutic purposes. Hippocrates does not report the use of oil for the treatment of intrapleural disease.

The use of oil for the therapeutics of intrapleural conditions is comparatively recent. It was first used for intraperitoneal pathological conditions and later its use was extended to the conditions of the chest.

This country deserves the credit of having the first reported use of oil for empyema. In 1914, at the suggestion of Ralph C. Matson, Kenneth A. J. Mackenzie (33) of Portland, Oregon, made a preliminary report on the use of paraffin oil in the treatment of empyema. It is unfortunate that Matson (34), who devised the method and suggested it to Mackenzie, is not even mentioned in the report. Mackenzie suggested that this form of therapy may be used in the treatment of tuberculosis and stated that

> its use might readily be extended to the treatment of tuberculosis of the lungs when the compression and fixation of the lungs are desired as a means of curing that disease. In this connection it might be substituted for nitrogen gas because it is not absorbed by the pleura, whereas nitrogen gas is irritating,

causes pleural effusion, and, because of absorption, has to be frequently replaced.

Details of the technique and an illustration of the apparatus for this work are included in this brief report. It is also unfortunate that this report has been buried in the graveyard of the literature, so that even a painstaking effort to get the reference in the *Index Medicus* led to a failure to find the article. A reprint of this article was kindly loaned to me by Dr. Ralph C. Matson, who casually spoke of his connection with the work, but is too modest to write about it. Therefore, with due recognition of the fact that Bernou (13) had coined the word "oleothorax" in 1922, we must admit that due credit must be given to Mackenzie and Matson for being the first ones to suggest and use eleothorax for intrapleural disease including tuberculosis.

The development of this form of therapy was gradual. It is a stepping-stone process as seen by the chronological arrangement of the work in this field.

1906: Wegner and Recklinghausen (4) showed that oil occludes temporarily the capillaries of the peritoneum.
1906: Glimm (5) published results on the resorption of oil in the peritoneal cavity.
1912: Camphorated oil was injected into the peritoneal cavity by Peiser (6), Hirsche (7), and Vignard and Arnaud (8), in order to prevent the formation of adhesions.
1914: Kenneth A. J. Mackenzie (33) of Portland, Oregon, presented to the American Surgical Association a "preliminary report on the method of treating empyema without resort to pneumothorax."
1915: Burnand (9) injected a small quantity of oil with gomenol into a pyothorax.
1916: Fournier (10) recommended the use of gomenol in oil for injection into the pleural cavity in serofibrinous pleurisy in order to shorten its duration.
1918: P. E. Weil and Loisseleur (11) used gomenol in oil in the treatment of pyopneumothorax.
1918: Cordier and Hinault (12) tried to prevent pleural adhesions by intrapleural injection of oil.
1922: Bernou (13) coined the term *oleothorax*, and injected a large amount of oil into the chest to induce collapse of the lung.
1922: Moigneteau (14), a pupil of Bernou, published a paper on the effectiveness of oil injections to prevent pleural adhesions and used it in the treatment of purulent tuberculous pleurisies.

1923: Thin (15) advocated eleothorax as an antiseptic and antiobliterative measure.
1925: Küss (16) made his first report on eleothorax.
1926: Küss gave a masterly summary of indications and technique for eleothorax.
1927: Hayes reported 2 cases of bronchial fistula and one of haemorrhagic pleurisy, all treated by means of eleothorax.
1932: Ray W. Matson (18) gave his masterly report on "oleothorax" in which he reported his results on 100 cases treated by this method.

In the last few years eleothorax has been assuming its proper place in collapse therapy of tuberculosis of the lungs. It is being used extensively in Europe and particularly in France and in a limited number of cases in America. This type of therapy has many advantages over pneumothorax and should be used whenever and wherever it is indicated. We believe, however, that, unless its various contraindications and complications of this treatment are definitely known, this mode of collapse therapy will go into disrepute very promptly, and it is for this reason that we wish to make a report of the reactions of the pleura and the lung to the various oils, both experimentally and clinically. We realize that failures in clinical cases are primarily due to improper appreciation of the changes produced by the oils in the pleural cavity. A very serious danger which has been neglected by those interested in this therapy is that of oil or fat embolism. The proper recognition of the clinical picture of fat embolism and its prevention will save many a life and keep this form of therapy in its proper respectable position. The greatest success of eleothorax therapy depends upon the proper selection of cases, the care taken to eliminate faulty technique, and the careful follow-up of the patient during the course of this therapy.

INDICATIONS

Eleothorax, whenever it is indicated, should be preferred to artificial pneumothorax because it is more lasting. Antiseptics may be used along with the oil. The number of refills is diminished to a minimum, thus doing away with the danger of complications incident to the course of artificial-pneumothorax therapy. Costa, Alcoba and Eonseca (20) state that eleothorax is preferable to artificial pneumothorax and consider the latter as the more dangerous.

Patients who are considered as possible subjects for eleothorax collapse must be only the ones in whom the lung has been partially or totally

collapsed by means of an artificial pneumothorax or an effusion. Eleothorax should be primarily considered in cases in which during the course of artificial pneumothorax the lung begins to expand gradually in spite of frequent refills or increases in intrapleural pressure. In such cases the injection of the oil should be done soon enough to avoid apposition of the parietal to the visceral pleura which may lead to fibrinous and later fibrous adhesions. As a word of precaution we wish to emphasize at this point the great danger of injecting oil in a chest when we are not certain if the needle is in the free pleural cavity, else a puncture or a tear may result in the lung. Such an accident would lead to the injection of oil into the lung structure with a possible resulting fatal oil embolism or a serious chemical or traumatic pneumonitis which may lead to abscess or gangrene of the lung.

Küss (16), in discussing the indications for eleothorax collapse, states that

> cases in which it is primarily indicated are ones of progressive obliterating adhesions in artificial pneumothorax. They may, of course, be treated by insufflations of air very close together and under very high pressure; but this treatment must be given in a hospital and is less effective than eleothorax. The gas pressure lowers rapidly, even with thickened pleurae that are not very absorbent, and as a result they have to be renewed at very short intervals with the disadvantage of great distention of the pleura and besides the pressure is not as stable as oil pressure.

Küss further states

> besides the oil acts as an antiseptic and is capable of killing the bacteria set free by pulling on the adhesions; the injections may be given further apart and give results better than those of frequently repeated insufflations of air under high pressure. Eleothorax is particularly indicated when the adhesions develop in cases complicated by exudate; in this case it acts on the adhesions by permanent pressure and also disinfects the exudate.

Munro (21), in a study of 20 cases of eleothorax, concludes that in tuberculous empyema, effusions blocking artificial pneumothorax, obliterative pneumothorax, and cases in which a compression produced by induction of air is insufficient, the procedure of choice is the injection of oil instead of air.

Matson (18) gives the following indications. He states that eleothorax is indicated in the course of pneumothorax therapy in the following cases.

1: As a disinfectant eleothorax for the treatment of pneumothorax empyema.
2: As an inhibition eleothorax (eleothorax antisymphysaire) to prevent expansion of the lung in cases in which a satisfactory collapse has not been maintained by air inflations because of a threatened early obliterative pneumothorax.
3: As a compression eleothorax to reëstablish collapse in cases in which air inflations have failed to maintain the proper collapse of the diseased lung tissue.

Among other indications of lesser importance Matson mentions

1: The collapse of rigid wall cavities in which an intrapleural pneumolysis is impossible.
2: Fixation of a labile mediastinum.
3: Gaseous tuberculous pleuritis as a prophylatic measure against empyema.

He also mentions a small pleuropulmonary fistula as an indication, but a large fistula he considers as a contraindication.

Dufault (3) states that the use of eleothorax is advocated in pleurisies, and in pleuropulmonary perforations, as a preventive against progressive adhesions, and as a means of compression. He quotes Küss stating that "the lung should not be allowed to macerate in bacillary pus which favors the softening of the cortical tuberculous pulmonary perforation. The oil blockage of the pleural cavity is the best method to assure prolonged compression and to heal sub-adjacent adhesions exerting at the same time an antiseptic action without causing any harm." Dufault further states that "the weight of the oil, by immobilizing the lung in the cases of pleuropulmonary fistula will give the fistula a chance to heal and at the same time dry up the pleural cavity. This condition, if untreated, will lead to asphyxia or decompression of the lung."

J. Fontaine (25) in her thesis recommends eleothorax in pleuropulmonary perforations and divides them into 4 groups: (1) the small, temporary perforations; (2) the check-valve type of perforation, in which the air passes from the lung into the pleural cavity or, less frequently, from the pleural cavity into the bronchus; (3) the large and permanent perforations; and (4) the perforations with intermittent manifestations.

Dufault (3) states that "the small perforations are most of the time symptomless and impossible to detect even by manometric readings. Only on the spontaneous collapse of the pulmonary stump can they be suspected. The explanation seems to be that such perforations are not in connection with a bronchus. They usually heal spontaneously." He

recommends eleothorax in the valvular type of perforation, especially if complicated by the presence of an effusion, as is often the case.

Oppengame (22) states that the indications for eleothorax are (1) to avoid adhesions; (2) to produce a more effective collapse when pneumothorax is unsuccessful; (3) to give more rigidity to the pleura if a bulging of the mediastinum occurs; (4) to close a perforation of the lung; (5) to change an empyema into a sterile disinfectant oil; and (6) in rare cases when social conditions make it difficult for the patient to continue with routine air insufflations. Oppengame states that the use of eleothorax is limited only to cases in which the perforation is a small one and has developed as the result of breaking of adhesions or a rupture into the pleural cavity of a small subcortical vomica not connected to the bronchus.

Courcoux and Bidermann (23) give for indications the following conditions, namely: progressive pleural symphyses in artificial pneumothorax, insufficient pulmonary collapse in artificial pneumothorax, and chronic purulent tuberculous pleurisy either primary or secondary to artificial pneumothorax. The authors further state that eleothorax is substituted for pneumothorax if pleural adhesions and a relaxed mediastinum form an obstacle to a complete collapse of the lung. In the case of pleural adhesions the permanent high pressure maintained by eleothorax is more favorable than the transient pressures of the renewed insufflations of air. In the case of a relaxed mediastinum the stable pressure of eleothorax, with a negative pressure and a slightly irritating effect of the oil, transforms the relaxed mediastinum into a resistant wall, which favors a complete collapse of the lung and against which an eleothorax with a positive pressure can be instituted if necessary.

Bernou (13) gives the following indications: He states that one of the most important indications is progressive pleural symphyses. When this condition develops early, the results of the pneumothorax are frequently compromised and it is necessary to have recourse to eleothorax. This intervention should aim at complete blockade, by sterilized olive oil or liquid petrolatum, of the residual cavity of the pneumothorax which is on the way to becoming obliterated. He further states that another indication for eleothorax is insufficient pulmonary collapse following pneumothorax when there are no adhesions but progressive elevations of gaseous pressure are without therapeutic effect. He continues saying that eleothorax is rarely indicated in serofibrinous pleural effusions. Only the serofibrinous pleurisies of the artificial pneumothorax with

persistent slight fever and incessant reproduction of fluid can be cured in this way. Eleothorax is indicated only in those cases of purulent tuberculous pleurisies which are severe in the beginning, or are secondarily aggravated, and which do not respond to other treatment. He further states that to avoid failures, eleothorax should be reserved for the pyothorax that follows a momentary pleurocortical evolution and an opening of a small focus in cases in which the collapsed lung does not contain any large lesions with a tendency to spread. With few slight variations the above indications are recommended also by Gilbert (24), Jacqueline Fontaine (25), Göbel (26), and others.

In the course of our pneumothorax routine we have found that in a group of patients who have adhesions, particularly those holding the apex, a mediastinal hernia develops after a time toward the opposite side. This hernia is always located at the level of the arch of the aorta and less frequently at the region of the *hiatus oesophageus*. A pneumolysis, whenever possible, will control this complication. There are some cases in which the adhesions are difficult to sever. In such cases we have found that the mediastinal pleura may be made tougher and thicker by injecting small amounts of oil at periodic intervals until the hernia disappears.

In classifying the indications as they appear in the literature we will have the following headings:

1: Pleurisies complicating artificial pneumothorax (Gilbert, Dufault, Courcoux and Bidermann, Matson).
2: Purulent tuberculous pleurisies to produce a disinfection of the pleura (Gilbert, Oppengame, Courcoux and Bidermann, Bernou, Burnand, Pruvost, Matson, Küss).
3: Pleurisies of certain types such as uncomplicated tuberculous effusions (Oppengame, Matson, Dufault).
4: Eleothorax as an essential substitute for pneumothorax (Gilbert).
5: Ineffective collapse of the lung due to insufficient compression with air (Gilbert, Oppengame, Matson, Dufault, Bernou).
6: To avoid adhesions in progressive pleural symphysis (*antisymphysaire*) (Bernou, Oppengame, Küss, Matson, Courcoux and Bidermann, Dufault, Göbel).
7: To produce a stable intrapleural pressure (Küss, Matson, Courcoux and Bidermann, Chandler and Gloyne).
8: In cases of obliterative pneumothorax (Gilbert, Küss, Matson, Courcoux and Bidermann, Chandler, Bernou, Dufault).

9: In cases of rapid absorption of air in artificial pneumothorax, so that the interval between the injections may become more prolonged because of the resultant slower absorption (Courcoux and Bidermann, Göbel, Pruvost).
10: To stabilize the mediastinum in cases of exaggerated mediastinal laxity and mobility (Dufault, Matson, Gilbert, Oppengame, Courcoux and Bidermann).
11: To close small pleuropulmonary perforations (Gilbert, Oppengame, Dufault, Küss, Courcoux and Bidermann).
12: To collapse rigid wall cavities (Matson, Dufault, Pruvost).
13: In patients who for some reason cannot arrange for frequent refills or artificial pneumothorax (Oppengame). This is considered as a contraindication by Matson.
14: As a preparation of patients with tuberculous empyema for subsequent thoracoplasty (Oppengame, Dufault, Küss).
15: To prevent late pleural reactions, including thickening of the pleura in the course of a prolonged artificial-pneumothorax regimen (Küss).
16: To prevent tuberculization of the pleura in the course of prolonged artificial pneumothorax (Küss, Matson).
17: In patients who develop febrile reactions during the course of pneumothorax collapse (Matson).
18: To induce eleothorax, a fully active pneumothorax or hydrothorax must be present (Göbel, Joannides).
19: To treat mediastinal hernia by causing a thickening of the mediastinum (Joannides).

In summarizing the indications for eleothorax we may include, therefore, a preceding pneumothorax; an effusion with or without pneumothorax; a rapid absorption of air leading to an obliteration of the pneumothorax collapse; the prevention of adhesions; an antiseptic collapse with medicated oils; the fixing of a mobile mediastinum, particularly in mediastinal hernia; and, finally, the collapse of rigid-wall cavities.

CONTRAINDICATIONS

Eleothorax being really a secondary step to an established artificial pneumothorax or pleural effusion should preclude a satisfactory collapse of the lung before any attempt is made to inject any oil into the chest cavity. If this rule is violated, dangerous and perhaps fatal complications may follow. These are (1) a chemical or traumatic pneumonitis with subsequent abscess or gangrene of the lung, and (2) fat embolism. It is, therefore, obvious that any conditions which are factors in contraindicating artificial pneumothorax should be regarded in the same light

as contraindications for eleothorax. Bernou (13) gives the following discussion with regard to contraindications:

The objections that have been made to the method are due to the difficulty and danger of oil injections and the fact that as eleothorax is generally given in very severe cases it is not always effective. But it is unjust to blame eleothorax for failures for which it is not responsible. For example, one of the clearest indications for eleothorax is aggravation of a cavernous tuberculosis treated by artificial pneumothorax under the influence of a pleural exudate. The development of these exudates, always rich in bacteria, the signs of toxic infection which they cause and the obstacles which they create to compression of cavities lead to the necessity for eleothorax. In many cases this gives excellent results in a very little while and the patient appears to be cured. But then after an interval of varying length the temperature rises, signs of suppurating cavity re-appear and in spite of increased pressure of the oil injections the results are not so good as at first. But the fault does not lie in the eleothorax but in the changes which have taken place previously in the pleura from the prolonged development of the pleural exudate. The tuberculous pleura may later retract, offering an invincible obstacle to the compressive action of the eleothorax and signs of cavity begin again. But even in these cases eleothorax is of value; it gains time, limits the bad effects of decompression, stabilizes the general condition and puts the patient in a better condition for surgical operation if necessary. Two important conclusions may be drawn from these facts: The first is that the danger of late pleural reactions in pneumothorax makes it particularly necessary to limit its duration: Many pleural exudates are due to the rapidity of the re-insufflations which makes it impossible to adapt the gas pressure to the exact indications in each case. The second is that it is better to give eleothorax early so as to prevent thickening or tuberculization of the pleura.

A very important contraindication for oil injections into the chest is a large pleuropulmonary fistula. It is generally agreed that a small pleuropulmonary fistula may be completely obliterated by the use of eleothorax. On the other hand, when a fistulous opening is of such a large size so as to allow the oil to get into the bronchial tree, the complications which may follow are obvious. The lung will be drowned in the oil with subsequent pneumonia which may cause even death.

The use of certain oils which may act as foreign bodies and irritants should be avoided as much as possible. The possibility of neoplastic changes in the pleura as well as in the lung from contact with paraffin oil must always be kept in mind. Paraffin oil has been used experi-

mentally to produce paraffinoma. Møller (29) and others produced experimentally in rats carcinoma of the lung by repeated tar-painting on the skin. It is obvious from such experimental data that any substance that may act as an irritant over prolonged periods of time may cause neoplastic changes in the lung or pleura. It is for this reason that in our clinical cases, on general principles, we use exclusively sterile olive oil, especially because this oil may be broken down into its various components and, perhaps, be even used by the body as food.

Among certain specific contraindications Gilbert (24) gives the following under three headings:

1: Acute serofibrinous pleurisy of febrile type. Gilbert states that one should never inject oil during the acute stages but always between attacks.
2: He hesitates to use eleothorax in purulent pleuritic fluid that has only a few bacteria but advises its use when the fluid is rich in bacteria. He recommends the use of 2 to 5 per cent gomenol in oil.
3: He advises against the use of indiscriminate eleothorax because a more careful and stricter regimen is necessary and, therefore, it should not be used as a substitute for pneumothorax in cases in which social conditions are such that the patient cannot come for frequent pneumothorax treatments.

Ballon (19) states that a large bronchial fistula should be considered as a contraindication for eleothorax. Göebel (26) considers eleothorax to be contraindicated in young persons or children who have cavities that do not collapse with artificial pneumothorax. Matson (18) gives the following absolute contraindications for eleothorax:

1: Pleuropulmonary fistula with a large opening
2: Ordinary serofibrinous exudate complicating artificial pneumothorax
3: As a substitute for pneumothorax in patients, who, for various reasons, are unable to undergo the prescribed course of pneumothorax therapy
4: Inability to maintain collapse on account of too rapid absorption of gas.

Matson further states that eleothorax is not to be recommended as a substitute for pneumothorax therapy, and believes that patients who for various reasons are unable to undergo the prescribed course of pneumothorax treatment should not have eleothorax because a more careful observation and a more strict regimen is required than in pneumothorax therapy.

We believe that oils which are not utilized by the body and act as foreign bodies such as paraffin oil should not be used in the induction and

maintenance of eleothorax. We know that a certain amount of oil is absorbed by the body through the pleura. If, therefore, globules of oil are absorbed which would act as foreign bodies in the blood-stream and the tissues, they are more likely to produce emboli or even perhaps neoplastic changes such as paraffinomata. On the other hand, oils which are used by the body, such as vegetable oils and, particularly, olive oil, when absorbed through the pleural surface, will be changed chemically so that they become innocuous and may even be used as a food by the body.

Eleothorax has not been successful in collapsing adherent apical cavities which would not collapse with artificial pneumothorax. Eleothorax, even with high terminal intrapleural pressure, has resulted in failures in such cases. In one of such cases we noticed a subcutaneous eleoma developing as a result of the high intrapleural pressure (plus 30 cm. of water). In a second case we noticed a dangerous displacement of the mediastinum to the opposite side, and had to aspirate enough of oil to bring the pressure down to plus 5 cm. of water. In such cases we believe a partial or complete thoracoplasty to be the procedure of choice. It is in such a case that an intraextrapleural supraclavicular apicolysis, as proposed by Joannides and Shapiro (30), may prove of value, particularly in patients who present contraindications to thoracoplasty.

To summarize the contraindications: We may say that eleothorax should be used only in cases in which there is a definite separation between the visceral and the parietal pleura with an interposing substance between them, such as air, effusion, or even pus. In all cases in which artificial-pneumothorax collapse is contraindicated, eleothorax should also be considered as contraindicated. Pleuropulmonary fistula of large size should be considered also as a possible contraindication for eleothorax collapse. The procedure is further contraindicated in cases of acute febrile serofibrinous pleurisy; cases of dense adhesions between the lung and the pleura; in patients who have an already overburdened circulation with low blood pressure, rapid pulse, anaemia, and damaged myocardium; and, finally, in patients with renal involvement, especially if metaphen or merthiolate is to be used for its antiseptic effect.

TECHNIQUE

Eleothorax technique is of greater importance than even that of artificial pneumothorax. The greater difficulty with which oil is injected into the pleural cavity and the possible dangers associated with accidents

that may occur during the injection of this oil, are the reasons for a safe technique. Furthermore, the reaction of the pleura to the various oils must always be kept in mind. The intrapleural pressure should not be allowed to rise any higher than 20 cm. of water or oil. Higher pressures than this figure may result in displacement of the mediastinum, injury to the lung, or leakage of the oil into the subcutaneous tissue, causing an eleoma of the chest wall. If Luer syringes with a capacity of 20 to 100 cc. of oil are used during the injection of the oil, it is important to hold the needle absolutely immobile. There is a tendency to lubrication of the tissues at the course of the needle. Such a condition sometimes causes the needle to slide in and out easily during the course of the injections, thus exposing the intrathoracic viscera to injuries and complications, such as perforation of the lung, or a puncture of the heart or large vessels with subsequent death from haemorrhage or oil embolism. When oil globules reach the blood-stream, because of the difference of the surface tension of the two colloids the oil globules remain as such until they reach the capillaries and then act as emboli. If a vital organ is thus involved immediate death may follow. It is for this reason that, after having experienced a number of fatalities in our experimental work, we were compelled to devise an eleothorax apparatus. This apparatus (figure 1) has been made for us by V. Mueller and Company of Chicago, and is supplied to the profession by them. It consists of two manometers, one of which is used to determine the pressure inside of the pyrex oil-bottle and the other to determine the pressure inside of the pleural cavity. This instrument is so devised that the oil is squeezed from a wide-mouth bottle into the chest cavity by increasing the air-pressure over the surface of the oil up to a definite point. We have found that if we use an 18-gauge needle, $2\frac{1}{2}$ to 3 inches long, and much like the one used for artificial pneumothorax, we are able to force the oil into the pleural cavity at the rate of two drops per second, when the air-pressure over the surface of the oil inside of the bottle is raised and maintained at a pressure of 250 mm. of mercury. The pressure of the oil at the point of injection is that of an atmosphere. A three-way valve is used with the syringe. One of these outlets being connected directly to the eleomanometer or hydromanometer so that, at any definite time, readings of the intrapleural pressure may be obtained by shutting off the oil-gauge and turning the stop-cock to connect the pleural cavity to the eleomanometer. If constant readings of the intrapleural pressure are required a separate

needle may be used at a level higher than the point where the oil is being injected. From this point a constant connection between the eleomanometer and the pleural cavity gives the variations of intrapleural pressure produced by the injection of the oil during the course of treatment (figure 2).

We find it quite important to avoid manipulating the needle after we

Fig. 1. The Joannides eleothorax apparatus

(Bottle made of pyrex glass to avoid breaking during sterilization. It is mobile and may be placed as close as possible to the patient. An extra bottle is provided for possible breakage and to prevent delay if more than one patient is to be treated.)

are certain that we are in the free pleural cavity, and thus we completely do away with the danger of possible injury to the intrathoracic organs. It is important that the position of the patient be such that the patient is lying flat on the table, either on his side or on his back. The table should be that of an inclined angle of 45 degrees, with the head higher than the feet. This manoeuvre makes it possible to allow the oil to drip

to the base of the chest-cavity. When an artificial pneumothorax is present, it is easier to allow expulsion of the air at definite intervals by disconnecting the oil-gauge at the point of the three-way valve. In such a case the needle should be inserted as high as possible. The amount of air expelled depends entirely upon the height of the intrapleural pressure during the injection of oil. Air is allowed to escape from the

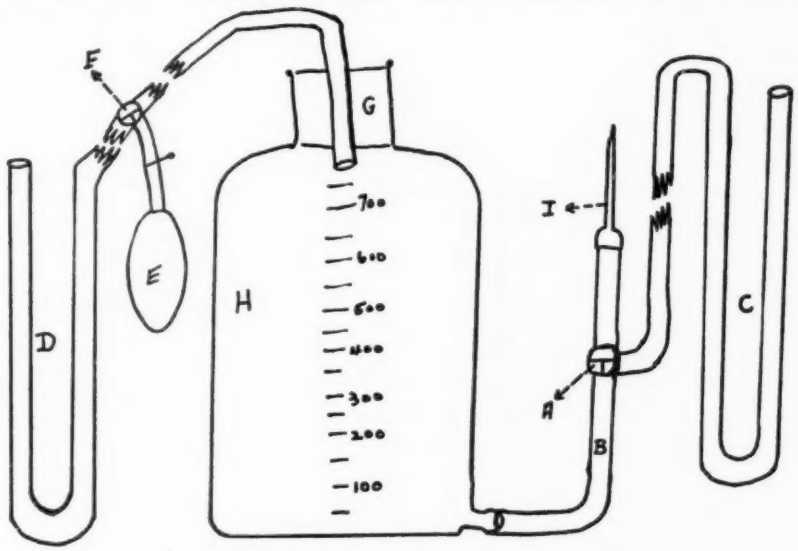

Fig. 2. Diagram showing details of Joannides eleothorax apparatus

A: Three-way valve to patient, bottle and manometer.

B: Short pure gum rubber tubing.

C: Eleomanometer for measuring intrapleural pressures—calibration in centimetres.

D: Mercury manometer for measuring pressure exerted over surface of oil. Calibration in millimetres of mercury.

E: Handpump.

F: Three-way valve to mercury manometer, oil bottle and atmosphere.

G: Rubber stopper.

H: Pyrex bottle calibrated in cubic centimetres of oil.

I: 18- to 13-gauge needle, 2½ inches long.

chest until the intrapleural pressure registers at zero or 1 or 10 cm. below zero. Oil again is injected until the intrapleural pressure again rises to a point of about 20 to 30 cm. of water, and then more air is allowed to escape from the needle. This manoeuvre is repeated, until the desired amount of oil is injected and a terminal intrapleural pressure of zero to plus 10 cm. water is reached.

For ambulatory eleothorax patients we adopted the following tech-

nique at the Collapse Therapy Clinic of the Municipal Tuberculosis Sanitarium. This routine has been carefully studied and approved by Dr. F. Tice, President, Board of Directors, and Dr. A. J. Hruby, Secretary of the Board.

1: Indications for eleothorax in each case are studied in a staff conference including Drs. M. Joannides, G. Tsoulos, V. Taglia, S. Narrod, L. J. Miller, and J. Taymor. No eleothorax is instituted until after a thorough study of the patient.

2: To determine the sensitivity of the pleura, injections of plain, neutral, sterile olive oil with 1–25,000 metaphen are used at 3- to 5-day intervals. Ten to 20 cc. are used for each injection. At least two test injections are made and an average of four injections.

3: The follow-up nurse, who sees the patient at his home on the same day, is instructed to watch for nausea, vomiting, chills, fever, malaise and to report any untoward findings to the Clinic or Dr. Joannides at once. A 4-hour T.P.R. record is kept by the patient. The nurse is instructed to report at once any undue tachycardia or rise of temperature higher than 99.5°F.

4: If any complications develop, a doctor from the Collapse Therapy Clinic is dispatched at once to investigate and give his personal attention. If the symptoms are rather acute, the patient is promptly hospitalized at the Collapse Therapy Clinic so that a closer observation is kept over the patient.

5: If no reactions follow the test injections, a larger injection of 200–500 cc. is given with the Joannides eleothorax apparatus after the third test-injection. This is repeated at 7-day intervals until the chest is filled.

6: In the cases in which the patient has an eleopneumothorax, the needle is inserted high enough so that air is allowed to escape while oil is being injected. In this way the intrapleural pressure remains within normal limits.

7: X-ray studies are made before each injection of oil. These aid in determining the degree of exudative reaction produced by the oil on both lungs. They show the degree of collapse obtained, and also the presence of any displacement of the mediastinum.

8: After the chest is completely filled with oil and the patient is symptom-free, he reports to the Clinic at 30-day intervals for study. In addition to the study of physical and roentgen signs, a needle is inserted into the chest to measure the intrapleural pressure. If the negative pressure is greater than minus 10, enough oil is injected to get it to zero.

9: When the chest is completely filled, the needle is inserted as low as possible to aspirate débris and effusion that may accumulate at the bottom. This is replaced with oil.

10: Patients with hydropneumothorax or pyopneumothorax are first aspirated and then an amount of oil equal to that of the exudate is injected. By in-

serting the needle low enough, the effusion is reached at its lowermost level. The aspiration is continued until oil begins to appear. At this point, the oil is injected.

In our experimental work we have used satisfactorily merthiolate in oil in a strength of 1 to 10,000 furnished to us through the kindness of Dr. Scher of the Municipal Tuberculosis Sanitarium. Unfortunately, however, it has not been possible to furnish us with a satisfactory solution of merthiolate in oil, with the result that we have used only metaphen in oil (Abbott), 1–25,000 in our clinical cases. We refrained from using gomenol or oil of cajeput because we found both these oils to be of the semi-drying type and irritating to the pleura. We have found in our experiments that caprokol in olive oil in a strength of 1–2500 is not irritating and can be well tolerated by the dog.

When the chest-cavity contains only a small amount of air and we are about to fill up the chest completely, we have utilized one of the two following methods. If the eleothorax is instituted in the patient's room where the bed cannot be tilted for any definite reason to assume a Trendelenburg position, we inject enough of oil to increase the intrapleural pressure to 20 cm. water. This step may cause a slight displacement of the mediastinum, so that when the air is allowed to absorb, the mediastinum will again resume its normal position. If the mediastinum is rigid, as the air becomes absorbed, the intrapleural pressure gradually diminishes.

Bernou (13) emphasizes the importance of measuring the oil-pressure and describes an eleomanometer designed by himself. He states that, in order to prevent febrile reactions, it is imperative to test the susceptibility of the pleura by an injection of a small quantity of oil. If there is no reaction, the blockade should be completed as quickly as possible in case of pneumothorax. He uses two syringes, one for the evacuation of air and the other for the injection of oil. After completion of the eleothorax, the loss of oil by resorption must be equalized by renewed injections. In cases of pyopneumothorax Bernou states that from 200 to 500 cc. of oil should be injected after complete thoracentesis. To avoid pleuropulmonary perforation he recommends that compressive eleothorax should not be induced in pleural cavities divided by adhesions or in cases in which the collapsed lung contains cavities with spreading disease processes. He maintains that perforations of the pleura most frequently result from evacuations of lesions in the collapsed lung. This, he says,

can be guarded against by watching the weight and the clinical signs, such as expectoration of tubercle bacilli, râles, fever, loss of weight, as well as roentgenological examinations of the variation between the volume of the cavities under eleothorax. Diehl (31), in discussing the technique in eleothorax, states that it is important to take into consideration the patient as a whole in the regulation of the intrapleural pressure. He believes that the patient should be in a sitting position during the injection of oil, in order that roentgenological determinations of the highest point of fluid collection may be determined, particularly in cases in which the mediastinum may be soft and displacement might result. He believes that positive pressures are indicated only in those cases in which considerable agglutination and adhesion of the pleural cavity have occurred. He states that the employment of moderate positive pressures only is required in these cases because the adhesions can be prevented only through complete separation of the two pleural layers. He recommends frequent roentgen examinations in order to keep accurate account of the degree of absorption of the oil so that possible obliteration of the pleural cavity may not follow.

Diehl (31) also emphasizes the necessity of collapsing the lung, keeping in mind the best possible preservation of the physiological relations. He states that the repletion of the pleural cavity with fluid, which, due to its weight and hydrostatic pressure, increasing with the depth, acts extensively upon the surrounding organs, involves even more than pneumothorax the danger of the induction of nonphysiological conditions in the thoracic cavity. He uses on an average of 300 to 500 cc. of oil for his injections, and pays particular attention to the variations of intrapleural pressures. He advises very strongly against an increased intrapleural pressure.

Küss (16) uses paraffin oil and gives the following reasons for his preference:

1: It can be easily obtained in a state of purity and keeps indefinitely
2: It can be sterilized at high temperatures without any special precautions
3: It has a high viscosity
4: It remains unaltered in the pleura
5: It is resorbed slowly.

Küss also believes that there is some antiseptic action on the part of this oil on the tubercle bacilli, and considers this fact of advantage, because frequently tubercle bacilli are set free in the pleural cavity during

the course of collapse therapy. He states that the resorption rate of the oil is from 8 to 15 cc. per month, even when the pleura has been modified by considerable exudate. He uses gomenol as an antiseptic with oil because he states that this substance has a marked bactericidal action on pathogenic organisms including the tubercle bacillus. He also states that gomenol has an additional advantage of being only slightly toxic and it is not caustic when used in an oily solution. After preliminary preparatory injection of 20 cc. of gomenolated oil and in the absence of any signs of intolerance he advises larger doses of oil until the pleural cavity is filled. He insists on injecting the oil at a temperature of 38°C., particularly when large amounts of oil are to be injected. The heating increases the fluidity of the oil and prevents chilling of the pleura. He advises a strength of 2 to 8 per cent of gomenol in paraffin oil and insists on using perfectly neutral oil, with a specific gravity of 15°C. of 0.880 and with a high viscosity. At 10°C. it should not become cloudy and should be limpid without fluorescence. Küss sterilizes the oil by heating it in flasks up to 150° to 170° from 15 to 20 minutes. The gomenol is added after the oil is cooled. He advises against the use of over 600 cc. of oil at one sitting. He uses two needles, which are so inserted that the oil is injected through the lower needle and, when the level of the oil reaches the point of the upper needle, then the oil is injected through the upper needle. Later injections to maintain pressure are made through a special syringe which is provided with a manometer to register the pressure at all times. If the pressure becomes too high, signs of intolerance will be noticed. In cases of hydropneumothorax or pyopneumothorax, Küss advises aspiration of the fluid, amounting to from 100 to 150 cc., and an equivalent amount of oil to be injected to replace the aspirated fluid. He contends that in cases of septic pleurisy, with artificial or spontaneous pneumothorax and with or without perforation of the lung, eleothorax permits obtaining a cure in the majority of cases in spite of the gravity of the prognosis, and the patient is spared from the risk of pleurotomy or thoracoplasty. In disinfection eleothorax he emphasizes his technique and proposes the following precautions, namely:

1: A vegetable oil containing 4 to 6 per cent of gomenol is preferable
2: The infected pleural fluid should be evacuated as completely as possible
3: The pleura should be irrigated with warm physiological salt solution
4: A sufficient amount of gomenolated oil should be injected
5: The operation should be repeated as often as the temperature rises. The oil should be evacuated and replaced by fresh oil each time.

Küss warns that great care should be exercised in the beginning when eleothorax is being induced. He advises the use of only 2 to 5 cc. of oil, and that a complete blockage should not be performed until it has been determined that the pleura tolerates the oil. He warns against injury to the lung which may lead to perforation, and speaks of this as one of the greatest complications of the method which often necessitates an emergency thoracoplasty. He quotes Bernou, who states that oil injections should be given without any positive pressure; in other words, keeping the pressure of the pleura about the same as the atmospheric pressure. Küss finds it necessary, however, particularly in cases of progressive adhesions, to maintain as high a pressure as 20 to 35 cm. of oil or even more. He states that if the necessary precautions are taken these pressures are borne without any bad results and their use enlarges the field of usefulness of eleothorax.

It is obvious from the foregoing statement that eleothorax technique possesses three factors, namely (1) the testing of the sensitivity of the pleura to the oil that is to be used; (2) the maintenance of low intrapleural pressures; and (3) the use of a technique which would limit the danger of injuring the lung or of increasing likelihood of subcutaneous injections of oil.

In our experimental work we have tried injecting the oil by means of a syringe attached to a needle. We have found that sudden deaths have occurred in the animals as a result of the oil being injected directly into the structure of the lung. At times we have also found that no oil was present in the pleural cavity, but was all localized in the subcutaneous tissues. These preliminary difficulties during the early part of our experimentation have impressed upon our minds the necessity of developing apparatus with which the injections of oil may be made without any undue effort on the part of the operator or the patient. Because the pressure determinations are obviously important, the apparatus had to have an attachment whereby intrapleural pressures in centimeters of water could be determined at any one time. By using a three-way cannula it is possible to connect the chest directly to the manometer and to the oil contained at any time without disturbing the needle any more than absolutely necessary. With the Joannides eleothorax apparatus, the oil is squeezed into the chest by exerting a positive pressure over the surface of the oil in an air-tight bottle. This pressure is exerted by means of a hand-pump, and is measured by means of a mercury manometer (figure 2). It is found that with an 18-gauge needle an amount equal to

two drops per second flows from the needle into the chest-cavity, when the pressure over the surface of the oil is exerted up to 200 mm. of mercury. The attachments are completely air-tight, so that a fairly constant pressure can be exerted over the surface of the oil. This instrument also has a water manometer which measures the intrapleural pressure. Frequent determinations of intrapleural pressure are made in order to be sure that the intrapleural pressure is never higher than 10 cm. of water. This rule has been established in our routine because of a serious pleurocutaneous oil fistula (eleoma), which developed as a result of our attempt to increase intrapleural pressure to a point sufficiently high (40 cm. of water) to collapse an apical cavity that had a definitely sclerotic wall which could not be collapsed by means of artificial pneumothorax. An increased intrapleural pressure may cause a sufficient amount of displacement of the mediastinum or even a tear of the mediastinum, causing a bilateral eleothorax. Furthermore, in cases in which adhesions are present, an increased intrapleural pressure may produce a tear of the lung, which, if large enough, may either produce a pleuropulmonary fistula or oil embolism. It is for these reasons that we believe that it is most advisable to maintain an intrapleural pressure not higher than zero or, at the most, 10 cm. of water.

One point in the technique of eleothorax which has not been sufficiently emphasized is the complete filling of the chest cavity with oil, particularly during the last sittings. In cases, in which eleothorax is being used to replace artificial pneumothorax, a large bubble of air remains over the surface of the fluid. This bubble gradually becomes smaller, as the fluid-level rises and the air is either aspirated or absorbed. Eventually it reaches a point where one cannot safely insert the needle high up without causing possible injury to the important vessels or intrapleural viscera. We have found it advisable to place such patients in a Trendelenburg position and, under the fluoroscope, determine the position of the air-bubble, which now is located not at the apex but at the base of the chest. The needle then is inserted over this area and the oil is used to replace the air at this area.

Clinically, we have found it advisable to take frequent X-ray plates to determine the degree of deviation of the mediastinum which will give us a fair index of the approximate intrapleural-pressure change and also the degree of absorption of oil from the pleural cavity. We found it always necessary to check up on the intrapleural pressure in our refills

and frequently noticed that as much as 100 cc. of oil is sufficient to raise the intrapleural pressure to a dangerously high point.

A very necessary precaution with reference to the use of rubber must again be taken into consideration. We have found that oil causes the rubber tubing to become gummy and eventually dissolve. For this reason it is necessary that all possible rubber tubing should be washed promptly, so that no oil be left in contact with the rubber which would dissolve the tubing and cause possible undesirable changes in the oil itself and deterioration of the rubber tubing. It is for this reason that in the Joannides Eleothorax Apparatus, which is prepared by V. Mueller and Company of Chicago, the rubber tubing which connects the oil-bottle with the chest-cavity is of the minimal length.

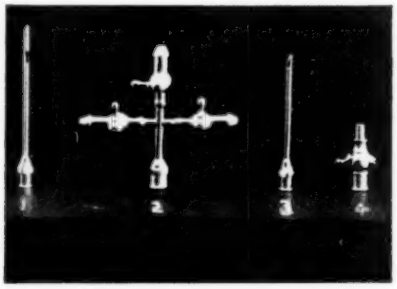

Fig. 3. Illustrating needles and stopcocks used by Matson for aspiration, irrigation and instillation of oil purposes. 1 and 3: thirteen-gauge needles. 2: four-way stopcock. 4: one-way stopcock. (The latest model is equipped with a Luer lock.) (Figure from the *American Review of Tuberculosis, 1932, xxv, 425.*)

Matson (18) has devised special needles and syringes (figure 3) which he uses for this purpose. He advises a technique very similar to that developed by Küss and others. He prefers gomenolated paraffin oil and has also suggested the use of irradiated oil. He is very particular about studying the sensitiveness of the pleura to the oil before he fills the chest-cavity with oil. He prefers to use a large syringe with a four-way cannula for this purpose (figure 4). We believe that, if a special apparatus such as ours is not available, the needle should always be attached to 10–20 cm. of rubber tubing and then connected to the syringe. It is then safe enough to use a syringe for this purpose because the needle will not be moved back and forth during the act of injection of the oil. If, on the other hand, the needle is attached directly on to the syringe there is a possible danger of moving the needle either forward

or backward. Injury of the lung or injection of some of this oil into the subcutaneous tissue outside of the pleural cavity may result. When this happens, an eleoma will develop and frequently perforate to the outside, producing a persistent fistula which is not only annoying but invites secondary infection. An eleoma is also likely to develop if one uses needles of a bore larger than 16- to 18-gauge. We noticed an eleoma develop in a patient of ours by the use of a 13-gauge needle. A fistula which develops from the use of a large needle may persist for several months. It is also a source of oil leakage, so that more frequent refills become necessary.

Matson, in discussing the technique of oil injections, states that, after

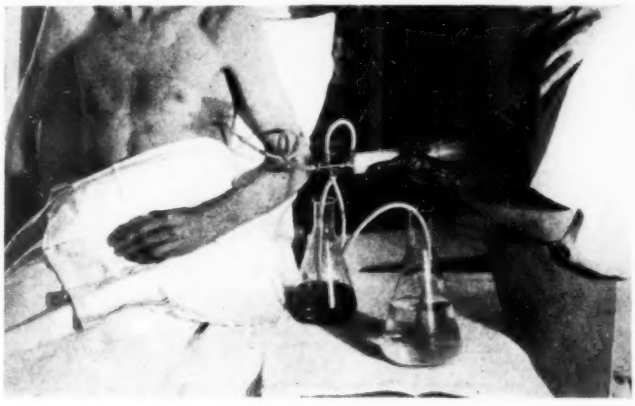

Fig. 4. Matson's technique by the use of syringe and cannula method

Note the rubber tubing between the needle and the syringe. (Figure from the *American Review of Tuberculosis, 1932, xxv, 433.*)

having determined by means of preliminary test-doses that the oil will be tolerated by the pleura, a complete blockade of the pleural cavity is accomplished in the following manner: The patient is placed recumbent in the dorsolateral position, lying on the healthier side. A small cushion is placed in the axillary region, so that a bulging of the chest is produced. A 13-gauge needle, armed with a one-way stopcock, is then inserted in the axillary region at the highest point of bulging. If small quantities of oil are to be injected, a 10-cc. or 50-cc. syringe is used. Otherwise, a 100-cc. syringe is filled with oil, and warmed to a point so that it will be delivered inside of the pneumothorax cavity at body temperature. Oil which is too cold or too hot is likely to provoke reactions. Furthermore, warming

of the oil facilitates injection by rendering the oil less viscid. After having connected the syringe with the stopcock, the valve is opened and 20 cc. of 1 per cent gomenolized paraffin oil is injected into the pleural cavity. The piston is then withdrawn, aspirating an equal volume of air into the syringe. This manoeuvre is repeated until the syringe has been emptied of oil and replaced with air. In this manner the desired quantity of oil is introduced to replace air which has been aspirated. The syringe is then disconnected from the stopcock, and the latter is connected by means of an adapter to the pneumothorax apparatus. The stopcock valve is next opened, and air, sufficient to bring the intrapleural pressure up to neutral, is allowed to flow into the pneumothorax cavity.

The injection of oil and the aspiration of air in units of 20 cc. is recommended in order not to disturb the intrapleural pressure greatly; otherwise, a severe febrile reaction might result. Furthermore, if the eleothorax is nearing completion, the injection of 100 cc. of oil at one time may bring about marked pressure phenomena, even causing a perforation into the lung if an area of softening exists in the pleura. It has already been stated that the quantity of oil injected is usually doubled at each sitting, but one should never exceed a dose of 400 cc. to 500 cc. in the adult male, or 300 cc. in women.

After many sittings of this sort, or when the eleothorax has been nearly completed, a fluoroscopic or radiographic examination of the patient in the erect position will show a small bubble of air at the top of the pneumothorax cavity. At the next sitting, this bubble is easily aspirated and replaced with an equal quantity of oil. The eleothorax is thus complete.

Eleothorax may be combined with thoracoplasty as suggested by Burnand (9), or with phrenic neurectomy as advocated by Bernou (13). Courcoux and Bidermann (23), in discussing their technique, indicate that they use olive oil or paraffin with an admixture of gomenol and eucalyptol. In their opinion, the eucalyptol favors the solution of the gomenol in the oily substance. The ratio of gomenol in their work varies between 2 and 4 per cent for a compressive eleothorax and between 4 and 10 per cent for a bactericidal eleothorax. They prefer paraffin for the compressive type of eleothorax because this substance has a greater viscosity than the olive oil. They use a needle of a calibre of 0.7 and a syringe of Küss's model which is provided with two outlets, one being connected with the needle and the other (lateral) with the oil-bag. The filling of the syringe is done by simply turning a cock. They emphasize

the importance of carefully watching the intrapleural pressure, which should be that of an atmosphere in ordinary cases and 30 to 35 cm. of water or oil in the cases of progressive pleural symphysis. In patients with purulent pleurisy, they inject 200–500 cc. of oil after a preliminary evacuation of the fluid and lavage of the pleura.

Chandler and Gloyne (28) use much the same technique as the previously described ones. They insist on pleural lavage in cases of purulent effusion. They recommend normal saline solution, flavine, or methylene-blue solutions for irrigation purposes. They recommend the use of large doses of oil, so that the chest may be filled at two to three sittings. To determine the degree of pleural reaction they study their patients by means of the X-ray. If effusion develops, they aspirate below the level of the oil, which remains at the top on account of its lower specific gravity. Courcoux and Bidermann (23) believe that frequent evacuations of the effusion and its replacement with the oil usually stop the reproduction of pus. They watched a purulent effusion of six years' duration transform itself into a serofibrinous effusion after two injections of 250 cc. of oil.

To summarize the technique of eleothorax, we must remember the following points:

1: Test the sensitivity of the pleura to the oil by using 10 to 20 cc. of oil for two to three sittings at three- to five-day intervals.
2: Use a needle not larger than 1-mm. internal diameter, even though it may take over one hour to inject from 200 to 500 cc. of oil. A needle with a larger calibre may result in the formation of a fistula and a subsequent development of a subcutaneous eleoma.
3: If an eleoma develops, never incise it, but aspirate at frequent intervals. An incision of the eleoma may result in an open pneumothorax which would prove disastrous to the patient. If a pleurocutaneous fistula develops shorten the interval between refills.
4: A small syringe can be used for the test injections of oil. For the injections of larger amounts, an apparatus of our own kind or that of Matson or Küss may be used. This precaution will prevent any undue manipulation of the needle after it is inserted into the pleural cavity. Thus, an injury to the intrathoracic viscera may be prevented. If an apparatus is not available, the only safe substitute will be to connect the needle to the syringe by means of about 20 cm. of rubber tubing. Thus, the needle will remain undisturbed during the injection of the oil.
5: The rubber tubing that connects the oil reservoir to the chest should be of

pure gum rubber, never red rubber, and must be of the shortest possible length that is practical.

6: With the Joannides apparatus an air-pressure of 250 mm. Hg. should be maintained over the surface of the oil in order to ensure a constant flow of the oil into the chest-cavity.

7: In the ordinary cases an intrapleural pressure of 0 or plus 10 cm. of water may safely be reached at the end of the injection. In the case of compression eleothorax this pressure may be allowed to rise to a point between 20 and 30 cm. of water. In such cases a radiographic check-up of the position of the mediastinum or the diaphragm should be insisted upon at frequent intervals (7 to 14 days) to avoid undue discomfort and possible perforation of the lung or the pleura, which may result in a pleuropulmonary fistula or a pleurocutaneous fistula with an eleoma of the chest-wall.

8: In cases of effusion it is best to aspirate the fluid at the lowermost safe point and inject an equal or lesser amount of oil to replace the fluid. The amount of oil injected should depend primarily on the degree of rise of intrapleural pressure during the injection of the oil. The optimum pressure is 0 to 10 cm. of water. When no effusion is present the needle should be inserted as high as possible, to allow for the escape of air from the chest.

9: Gomenol in a concentration of 2 to 10 per cent has been used with or without eucalyptol. In our work we find gomenol to be irritating to the pleura. Because of its pentrating odor, it becomes very annoying to patients with a pleuropulmonary fistula. Based on the results of our experiments, we are using metaphen in oil (Abbott) in a concentration of 1:25,000. Such a concentration is not likely to produce any renal involvement through its mercurial content. Merthiolate in oil (Lilly) has been used successfully in our experiments and has proved as satisfactory as metaphen. Caprokol in oil, in a concentration of 1:2500, has been satisfactory in our experimental work. Corn-oil and peanut-oil were too irritating to our dogs. We have not tried them clinically.

10: The position of the patient should be much the same as in artificial pneumothorax. We prefer a tilting table, so that we may at will raise or lower the head of the table as the indications arise. We usually keep the table tilted to an angle of 45°, thus keeping the head higher than the feet.

11: A suction pump or a Potain aspirator should be kept handy to aspirate the pleural contents or the oil in cases of undue increase of pleural pressure. A thoracotomy should never be done, because it will produce the same effects as a thoracotomy in a case of an acute empyema. The obvious results of such a step were emphasized by Graham and his co-workers (32) during the World War at the time of the influenza epidemic.

12: The patient should be prepared in the same manner as for artificial pneumothorax. The skin may be sterilized with any one of the common anti-

septics. We prefer tincture of iodine. A small amount of 1 per cent procain (1 to 2 cc.) should be used to anaesthetize the skin and subcutaneous tissues.
13: After the injection of the oil the patient should be watched for possible signs of shock resulting from oil embolism. If this happens, repeated injections of 5 to 15 minims of 1:1,000 solution of adrenalin should be given in the hope of squeezing the oil globules from the capillaries into the tissue cells and of preventing possible embolism of the medullary centres or the coronaries. For further details on fat embolism the reader is referred to the discussion of this topic under *Complications.*
14: We believe that eleothorax should be given to the patient in the hospital. It may be given at home provided there is a nurse in attendance who could watch for complications.
15: We feel it safe enough to give eleothorax to ambulatory patients if they are allowed to rest and stay under observation for at least 6 hours after the injection of the oil.

CLINICAL RESULTS

The clinical results that one hopes to obtain are a more even and lasting collapse of the lung, with the interval between the injections extended to the greatest safe maximum. Eleothorax can produce a rigid mediastinum in patients who, because of a labile mediastinum, cannot sustain a satisfactory pulmonary collapse with air. In fact we have been able to change experimentally the thin cigarette-paper-like mediastinum of dogs into a thick resistant wall, thus separating completely the two hemithoraces of the dog (figure 5). It is believed by many that oil in combination with antiseptics, such as gomenol, acts as a disinfectant in pleurisies with effusion or in pyothorax. We doubt that any appreciable antiseptic effect can occur through the contact of the two fluids with each other. This is obvious when one remembers the difference in the specific gravity of the two fluids. The oil naturally remains on top and the pus or effusion at the bottom. The mild churning that occurs by virtue of the respiratory movements is not sufficient to produce a bactericidal effect Experimental checks on the growth of microörganisms in the exudate from the chest has convinced us of this fact.

The bactericidal effect of eleothorax in cases of pyothorax or effusion is due to the contact of the antiseptic oil with the infected pleural surfaces, so that the pleural infection subsides and the exudation is diminished. If, then, by repeated aspirations, the infected fluid is removed and an antiseptic oil is injected, one can eventually sterilize the pleural surfaces entirely.

Gilbert (24) emphasizes the detoxicating effect of eleothorax and attributes it to the anatomical modification of the pleural layers, so that the absorption of toxins becomes diminished. This thickening takes place also on the mediastinal surface and this fact may be utilized for the prevention or treatment of mediastinal herniation or displacement (figure 5).

Courcoux and Bidermann (23) emphasize the importance of the "oily

Fig. 5. Eleothorax in the dog. Note the mediastinal and pleural thickening. Left chest completely clear.

blockage effect" as described by Bernou (13) used to prevent pleural symphyses. Of 39 cases of eleothorax instituted for this indication, they report 26 as effective, 4 ineffective, and 9 fatal (five being due to pulmonary perforation). Of 32 cases instituted for purulent pleurisy, 15 were effective, 2 ineffective and 10 fatal, due to therapeutic failure, while 5 died from causes independent of the eleothorax.

Matson (18) reports the following results in 50 cases of disinfection

eleothorax, alone or combined with an inhibition or compression eleothorax: Satisfactory results such as the clearing up of empyema in 60 per cent of the cases. Of the failures (40 per cent) or 20 cases, 4 developed pleurocutaneous fistulae, 4 developed pleuropulmonary fistula, 8 failed to show disinfection of the pleura, and the last 4 showed a reformation of the exudate, thus necessitating the abandonment of the eleothorax collapse. In his 50 cases of inhibition or compression eleothorax, Matson noticed satisfactory results in 25 cases (50 per cent). In the group of failures the treatment was temporarily abandoned, but successfully reëstablished in 15 cases (30 per cent) and permanently given up in 25 cases (50 per cent). The abandonment of the eleothorax was necessitated in 20 cases because of a persistent exudate formation and in 5 cases because of severe constitutional reactions.

That oil is absorbed into the general circulation is shown by Chandler (28), who reports that it was taken up apparently by the cells lining the pleura; a lipolytic action took place and the oil, he imagined, was used as food. If an oil such as lipiodol was injected into the pleural cavity, the iodine fragment was liberated and could be detected in the urine. He further states that "the rate of absorption was roughly known: olive oil might be completely absorbed in six months, and paraffin oil in from 12 to 18 months." Chandler states that he does not employ liquid paraffin because in one case it appeared to irritate the pleura.

We believe like Chandler (28) that the rate of absorption of oil is not as yet controllable, because we do not know how such an absorption may occur. In a series of blood determinations for the presence of oil in the blood our results were negative. The determinations, made by an expert chemist under the supervision of Dr. H. C. Sweany in the Research Laboratories of the Chicago Municipal Tuberculosis Sanitarium, showed a quantity of oil of insufficient amount to measure and test chemically. Furthermore, determinations of the iodine number and the saponification number of the oil, after it remained in the chest of dogs over varying periods of time, showed no appreciable changes. It is obvious, therefore, that the mechanism of oil absorption through the pleural surface must be determined by more sensitive analytical methods, possibly microphysicochemical.

We have made a crude effort to determine the extent of absorption of the oil through the pleura by inducing an eleothorax in the dog and using Sudan-III as a coloring matter. We have been able to trace the Sudan-III in the bronchial lymph nodes. Thus, we may reasonably

assume that the oil is most probably absorbed through the lymphatics and then enters the general circulation, either in its original form or changed into a more assimilable substance. It is for this reason that it would seem logical to use a vegetable food-oil such as olive oil, so that its absorption may not cause any pathological changes in the body.

Experimentally, we have tried also corn-oil, peanut-oil, and also medicated and nonmedicated vaseline, but all these substances were found to be unduly irritating to the pleura. They caused a prompt and fatal pleurisy with effusion. We hoped that unsaturated oils like peanut- and corn-oil would be nonirritating, and thus enable one to inject harmless iodine combinations of these oils and make our roentgen visualizations better. Unfortunatly, we were compelled to abandon these substances and carry on with olive oil, plain or medicated.

COMPLICATIONS

The complications worth considering in eleothorax therapy are fat embolism, pleuropulmonary fistulae, pleurocutaneous fistulae causing eleomata, irritation of sensitive pleura causing effusion, and, finally, constitutional reactions best grouped under the symptom-complex evident in influenza, in addition to rapid and progressive loss of weight and marked pallor.

Oil or Fat Embolism

One of the great and least-emphasized dangers of eleothorax therapy is fat embolism. We refer to this complication as "fat embolism" rather than "oil embolism," because the term "fat" is generic and includes oils which are fats of lower melting point. This complication has not been satisfactorily emphasized, and all references made to fat embolism refer to the condition resulting from the injuries to bones. Fat embolism is generally the cause of peculiar unexplainable deaths when the animal or patient gradually goes downhill, the pulse becomes rapid, anaemia results, and finally death ensues. The onset of fatal symptoms depends entirely on the amount of oil and the size of fat droplets that find their way into the general circulation. It must be remembered that the oil and the blood are two colloids of different surface tensions, so that they do not mix under ordinary conditions. Drops of oil in the blood remain globular and are carried as foreign bodies (emboli). They eventually reach the liver, where they become changed and absorbed. If the drops of oil are sufficiently large to plug the terminal capillaries of the vital organs or

medullary centres, the animal or patient dies very promptly, and the symptom-complex depends entirely upon the part of the body that comes in contact with the globules of oil. It is for this reason that it is necessary to use oil that can be easily hydrolyzed and oxidized in the body, and thus used up like the rest of the fatty substances. Obviously, therefore, liquid paraffin is a dangerous oil to use from this point of view. Furthermore, it is necessary that the oil be of a surface tension very similar to that of the blood. If this could be accomplished, then the two colloids might diffuse sufficiently, so as not to act as foreign bodies toward each other. One precaution necessary from a technical point of view is the advisability of using a small-calibre needle, generally never greater than gauge 16, so that, if any oil droplets accidentally find their way into the tissues, they will not cause large globular emboli and kill the individual.

Clinically, Vance (35) recognizes two distinct and well-defined clinical and pathological varieties of fat embolism, namely, the pulmonary form and the cerebral form. In our experimental work we have been able to recognize a third form, namely, the cardiac form. Vance describes the pulmonary form as one in which the emboli obstruct the smaller blood-vessels of the lung and produce symptoms of asphyxia. He classifies as of cerebral type the one in which the emboli gain entrance to the arterial circulation, block the arterioles of the different organs, especially the brain, and produce symptoms referable to the nervous system. In the cardiac type we have found a blocking of the coronaries resulting in arrhythmia, circulatory collapse, anginal attacks and, eventually, death from myocardial anoxaemia or asphyxia.

Pulmonary fat embolism has been classified by Grondahl (36) also into two groups. The first type is characterized by a sudden onset of dyspnoea attended by marked cyanosis and oedema of the lungs. These symptoms develop within a few hours after an injury which may cause a fat embolus to be liberated. Death results rapidly in this type of a case. In the second group, the onset is slower, and it may even take several days after an injury before the symptoms develop. There may be some restlessness, and a persistent cough associated with bloody sputum. As said, there is also dyspnoea, cyanosis and signs of pulmonary oedema. Toward the end, the respirations become stertorous and gradually change into the Cheyne-Stokes type. This type terminates in a fatal coma. The pulmonary type of fat embolism is apt to occur in cases of myocardial degeneration and pulmonary emphysema.

Vance prefers to classify all other types of fat embolism as of systemic

or cerebral type. He states that a number of fat emboli may pass through the pulmonary circulation into the systemic circulation and thence to all organs or tissues of the body, especially the brain and the kidneys. When the cerebral vessels are involved, according to Vance, the symptoms may be divided into three stages. These may fuse into one another or may stand out as distinct stages.

In the first stage, the period between the trauma and the first appearance of symptoms, there are no gross symptoms. This period may extend from 4 hours to 10 days. We might refer to it as the dormant period.

The second stage may gradually set in or it may come on rather dramatically. It is characterized by dyspnoea, restlessness and precordial pain as the premonitory signs which fuse into those of localized cerebral manifestations. These are insomnia, loss of memory, disorientation, and a mild delirium. After a variable interval the patient sinks into a stupor and gradually passes over into the last stage, that of coma, which gradually becomes deeper and results in the death of the patient.

Vance has described in detail the pathological manifestations of fat embolism and for those particularly interested we recommend a further study of his article.

In a statistical study, Killian (37) has reviewed the literature. He found that, in a period of 21 years extending from 1909 to 1929, fat emboli occurred in 0.16 per cent of 70,000 hospitalized patients at the University of Freiburg. Up to 1924 the annual number had been 3 to 4 fatal cases, but afterward a rapid increase followed up to a maximum of 17 per year. Killian attributes this increase to a larger number of accidents in recent years. Fat embolism occurred most frequently between the ages of twenty and fifty. Ninety-two per cent of the subjects were males.

Clinically, Killian has found that regardless of whether the embolism occurs separately in the lesser circulation, or both the pulmonary as well as systemic systems, the chief general sign of fat embolism is elevation of temperature and acceleration of the pulse. Very soon afterward, from 6 to 36 hours, the typical pulmonary or cerebral manifestations follow. He found no aetiological relationship between fat embolism and *Status thymolymphaticus*. Killian finds a distinct relationship between shock, haemorrhage, and fat embolism. Out of 112 cases reviewed, only 2 cases were without shock.

In the diagnosis of this condition Vance (35) emphasizes the difficulty of confusing fat embolism with intracranial haemorrhage complicating a

skull fracture. He states that in typical cases the two should never be mistaken, because the intracranial haemorrhage is most often attended by signs of cerebral compression and definite neurological signs referable to the site of the lesions. On the other hand, these syndromes are absent in cases of cerebral fat embolism, and lipuria, petechial haemorrhages of the upper parts of the chest, and an ophthalmological demonstration of the emboli in the retinal vessels may help to establish the diagnosis.

Experimentally, Killian (37) has found that the dissemination of from 12 to 20 gm. of fat into the circulation always causes death by blocking the circulation. This he determined by studying the fat content of normal lungs and those with fat embolism. We have found in our experiments that the size of the globule is of greater importance than that of the amount. As little as one cubic centimetre of oil injected rapidly into the vein of a dog would cause rapid onset of symptoms. On the other hand, by the slow injection of small amounts of oil, 1 to 2 cc. at a time so that only a few fat droplets were introduced into the blood stream from a 22-gauge needle, as much as 120 cc. were injected before the onset of fatal embolism.

EXPERIMENTS

In our experiments we used plain neutral sterile olive oil. We used the femoral vein in all the dogs. Protocols of 12 such experiments are recorded briefly:

Intravenous Oil

Dog 32: June 7, 1932. Under ether anaesthesia, 7 cc. olive oil into femoral vein, quickly. In three minutes, which was the time by which 7 cc. was injected, dog stopped breathing. No complications. Autopsy showed dilated heart, oil emboli in vessels of heart muscle, and bubble of oil in blood.

Dog 36: May 19, 1932. Ether anaesthesia. 125 cc. cold sterile olive oil injected slowly into right femoral vein. Developed shock; pulse irregular. Respiration and heart stopped simultaneously. Injection took 15 minutes, 22-gauge needle.

Dog 38: May 31, 1932. Novocain anaesthesia. Injection of 50 cc. plain olive oil into right femoral vein. Death in 10 minutes, the time required for 50 cc. to be injected. Injection stopped after symptoms developed. Dog well, till suddenly developed opisthotonos, sweating in paws. Heart and lungs stopped apparently at same time. Pulse slow and weak, but not irreg-

ular. Autopsy shows blood-stream full of oil-bubbles. Blood coagulates within one minute; white patches in lungs with petechial haemorrhages. Oil-bubbles come out of vessels of spleen, liver. Bronchi and trachea filled with foamy saliva.

Dog 39: June 2, 1932. Novocain anaesthesia; left femoral vein; 50 cc. olive oil into vein. Dog restless when 30 cc. injected in 3 minutes; developed generalized tetanic convulsions with opisthotonos. Head jerked to right, coma immediately followed, and respiration stopped. Incontinence of urine during convulsions. Heart kept beating for over an hour after injection of oil; heart kept beating after chest opened. Arrhythmia. *Autopsy:* Hypermotility of oesophageal and intestinal smooth muscle with both downward and constricting contractions. Intermittent contractions in excised oesophageal and heart muscle. Bubbles of oil in blood-stream; blood coagulates very promptly. Layering of blood cells at bottom; bloody oily layer in middle, and clotted blood at top. Striated muscles also show hypermotility.

Dog 44: June 10, 1932. Ether anaesthesia. 14 cc. into left femoral vein. Dyspnoea after 6 cc. in 3 min. Arrhythmia at this time. Pulse down to 52. In 9 minutes, 6 cc. more or total 12 cc. caused nystagmus, lateral and rotatory. Convulsion, with incontinence of urine and faeces. Pulse now down to 44. Three minutes later, when abdomen opened, bowel found atonic, but striated muscle shows clonic contraction. Two more cc. of oil into vena cava in abdomen and dog promptly stopped breathing. Three minutes after "death," hypertonic contractions of bowel. Emphysema of lungs. Foamy frothy contents in bronchi.

Dog 45: June 13, 1932. Novocain; 25-gauge needle. Left femoral vein. Pulse 180, went to 78, and irregular when 30 cc. injected. By this time shallow respirations, with occasional gasps. Pulse went down to 50 when 35 cc. injected (plain olive oil). Stopped breathing 20 minutes after 35 cc. given, and 34 minutes after onset of injection. *Autopsy:* Dilated heart, lungs expanded with patches of white areas which changed to gray color on exposure to light and air. Globules of oil in blood. Blood clots readily.

Dog 47: June 20, 1932. Novocain. Femoral vein. Pulse 120 at onset. 68 cc. olive oil in 25 minutes. Pulse down to 42 and stopped 5 minutes after injection ceased. Injection stopped when tetanic convulsion occurred. Dog dyspnoeic; incontinence of urine and faeces. *Autopsy:* Heart dilated; oil in blood-stream. Blood coagulates quickly on removal from vessels.

Dog 48: June 23, 1932. Right femoral; novocain. Pulse 150 at beginning. 90 cc. injected in 37 minutes. Pulse slower until, when 50 cc. injected, went

down to 80. By time rest of 40 cc. injected, convulsion with incontinence of urine and faeces and gasps for breath. Contractions of foreleg and neck muscles. Stopped breathing in 5 minutes. Oil droplets from vessels of all organs, including heart and lungs. Blood clots readily on removal from vessels.

Dog 49: June 24, 1932. Right femoral vein. Novocain. Pulse 140 at onset. In 6 minutes, 25 cc. of olive oil injected with large-calibre needle. Dog went into shock, no convulsions; and stopped breathing 4 minutes after injection was stopped, or 10 minutes after beginning of injection. *Autopsy:* Oil droplets in blood-stream and abdominal organs; petechial haemorrhages in lungs; heart dilated.

Dog 66: June 17, 1933. Ether. Left femoral vein. 70 cc. intravenously in 7 minutes. No convulsions. Complete relaxation. Oil globules in blood. Persistent clonic contraction of longitudinal and circular muscle of oesophagus. Bladder filled with urine.

Dog 67: June 24, 1933. Ether; left femoral. 120 cc. of plain olive oil intravenously. Dog into complete atonia and stopped breathing. Heart dilated; oil globules in blood-stream and vessels of organs.

Dog 71: August 1, 1933. Ether; left femoral vein. Sudan-III in oil to determine exact fate of oil. No convulsions. Shock, dog stopped breathing. Sudan-III mostly in liver. Sudan stain in vessels of lung and heart muscle. Large oil embolus in one of larger pulmonary vessels.

Certain interesting facts may be noted from these experiments. None of the dogs presented the same picture. In our experiments we continued injecting oil until symptoms were noted and then we promptly stopped. The time between the onset of symptoms and death was very short, and in some cases death was almost immediate. At autopsy samples of blood were shown to have oil of varying amounts. The oil became evident after the blood was allowed to stand for a few hours to a few days (3 to 4 days).

In vitro we have found that, because the oil and blood have different surface tensions, they never mix, but have a tendency to stay in small globules. For instance, if we place a few drops of oil in 10 cc. of blood, or *vice versa*, and after thorough mixing we allow the sample to stand, we notice that globules of varying sizes float in the test-tube and stay there as separate units. This phenomenon becomes more obvious when

a few drops of blood are mixed with about 10 cc. of oil. On shaking, the blood droplets will break down to smaller globules, and assume a place at various levels of the oil. These droplets will always stay as distinct units until there is complete coagulation of the blood.

The droplets then appear as distinct beads and, if allowed to stand in the test-tube for 3 to 4 days, they settle to the bottom but have a tendency to remain as distinct coagulated pearls.

These experiments lead us to assume that oil may act as a foreign body if introduced into the body as large droplets. We have a certain amount of fat in our circulation at all times. This fat, however, is introduced into the blood-stream in an assimilable form, so that it may be hydrolyzed or oxidized in the cells. We hope soon to make a further study of this subject in order to determine the smallest-sized globules possible that can cause fat embolism. We believe that, if we use an oil that can be oxidized by the body cells and introduce it in globules of the size of the red blood cells so that no obstruction will occur in the capillaries, we may be able to inject large amounts of oil into the circulation with perfect safety.

The treatment of this condition is distinctly preventive. Just as in air embolism, so is it in fat embolism. After the onset of symptoms, there is no way of getting rid of the large globules of oil that have lodged in important or so-called vital organs. If necessary precautions are taken, this complication in eleothorax will and should remain only a theoretical consideration.

Among others who have written on this subject we should mention Aievoli, E. Burns, Burnier, L. Burns and Bromberg, Culver and Baker, Dennis and Work, Dietrich, Elting and Martin, Flick and Traum, Gajzago, Gauss, Grondahl, Klapp, Menestrina, Miloslavich, Orseni, Patterson, Tobler, Lehman and Menattin, and Paul and Windholz.

This neglected subject is well worth every one's attention in eleothorax therapy and its prevention is worth the effort. It should be also a word of warning for those who often use various oily preparations intramuscularly or intravenously for therapeutic purposes.

DISCUSSION OF OUR EXPERIMENTS

The bulk of the experimental work was performed on the dog. In the first few experiments we used rabbits and guinea pigs, but these animals did not prove as satisfactory as the dog. Our main difficulty at first lay in producing a unilateral eleothorax. Because of the very thin

anterior mediastinum in the dog, the material found its way into the opposite side of the chest, and invariably a bilateral eleothorax resulted. This fact made our experiments uncontrollable, because of pressure exerted on both lungs, with eventual death of the animal from asphyxia.

The very first problem to be solved, therefore, was to find some means of causing a thickening in the mediastinum, so that one side of the chest would be somewhat independent of the opposite side. Plain oil alone did not produce a sufficient amount of pleural thickening to do any good. Peanut- and corn-oil, which were more irritating, produced so considerable an amount of effusion as to warrant against their use for that purpose. Gomenol or oil of cajeput mixed with plain olive oil or mineral oil proved to be far more irritating than peanut- or corn-oil. Turpentine with oil was found to be still more irritating, and the dogs died of an acute pneumonia with a massive bilateral effusion. The one irritant which proved most satisfactory was chlorpicrin (tear gas). After using varying concentrations of chlorpicrin in olive oil, we noticed that one drop in 100 cc. of olive oil was sufficiently irritating to produce a thickening of the pleura and the mediastinum. In this way we were able to imitate conditions quite similar to those in the human being. Stronger concentrations of tear gas produced a severe fatal pneumonia. In such cases the animal died in shock in a few hours, and at autopsy a haemorrhagic type of pneumonitis with pleurisy was evident. Chlorpicrin in oil was first tried on October 13, 1932, but not until January 10, 1933 were we able to produce a successful thickening of the mediastinal endothelium. The following is a brief protocol of this experiment.

Dog 62: Red setter, 15 lbs. Ether anaesthesia. Chlorpicrin in olive oil (10 drops to 250 cc. of oil) injected into right chest on January 10, 1933. On January 17, 1933, 50 cc. merthiolate in corn-oil, 1:5000, into right chest. No struggle. Dog in good condition at end of injection. Injections repeated as follows: 100 cc. on January 24, 1933; 100 cc. on January 31, 1933; 85 cc. on February 2, 1933. Dog found dead on February 8, 1933. Was in apparent good health except for dyspnoea one hour before death. Dog died of oil embolism as revealed at autopsy. Pleurocutaneous eleoma at site of last injection. Oil bubbles in liver and spleen. No free fluid in peritoneal cavity or left pleural cavity. Right chest shows complete collapse of lung. Definite carnification of lung. Mediastinum and pleura 2 mm. thick. Strands of adhesions of eleogenous exudate. No exudate in pericardial sac. Microscopic examination shows emphysema of left lung and stria formation of the interstitial elements of the right lung.

The materials used for these experiments were kindly supplied by various pharmaceutical companies who coöperated with us in every respect. The olive oil used for our experiments was supplied through the kindness of E. R. Harding by the H. J. Heinz Company of Pittsburgh. An analysis of their oil was as follows: Specific gravity at 15.5°C., 0.9149; refractive index at 15.5°C., 1.4710; acidity as oleic acid, 0.48 per cent; iodine number, 81.6; saponification number, 183; free from cotton-seed oil and sesame oil. Caprokol in oil was supplied by Dr. G. H. Krall, Medical Director, Sharp and Dohme of Philadelphia. Metaphen in oil was furnished by Dr. J. F. Biehn of the Abbott Laboratories of North Chicago, Illinois. The merthiolate was given by Dr. Karash, through Dr. Sher, Chief Chemist of the Municipal Tuberculosis Sanitarium. An ample supply of corn-oil was sent to us from Meade Johnson and Company.

In the olive-oil series plain neutral sterile oil was used. After a preliminary chlorpicrin injection to thicken the mediastinum, varying amounts of oil were injected. The average total amount was 300 cc. with a maximum of 900 cc. The average dose was 100 cc. of oil at intervals of 3 to 14 days. These dogs were left alone, and nothing was done beside the oil injection so that we eliminated every possible extraneous factor. All animals were not disturbed till they died. Some of these animals lived as long as six months after eleothorax was established. Twelve animals were used for this series. At autopsy the pulmonary collapse varied from 50 to 95 per cent and depended upon the amount of oil injected. In 4 out of 12 dogs a fatal effusion developed on the opposite side. The effusion was serous or serosanguineous. No pus was present in any of these dogs. In no case did the oil produce any changes in the peritoneal cavity. On the eleothorax side there was a thickening of the visceral and parietal pleura with strands of adhesions covered by an oily exudate.

In practically all our experiments there was a definite layer-formation in the oil. On getting samples of the exudate from the eleothorax side the sample separated into three distinct layers. This layering developed after the sample was allowed to stand for 2 to 48 hours. There was a thick gray layer at the bottom. This was mainly pus cells and cell débris. The middle layer showed an emulsion of oil and serous fluid and varied in color from gold yellow to bloody. The top layer showed a layer of clear oil.

The practical clinical value of this phenomenon is interpreted in the

fact that sediments can be aspirated from the dependent portions of the patient's chest until one strikes clear oil. A refill can then be made with fresh oil without the necessity of pleural washings or wasting of oil.

Another important clinical fact that is cleared up by this observation is the correction of the misconception that antiseptic oils may sterilize the effusion. In spite of evidence of slight churning of the oil in the chest, the main bulk of the oil tends to stay at the top, while the infected materials are found in the lowermost layer of the fluid. It is obvious, therefore, that the lower surface of the oil is the only part that comes in contact with the upper surface of the exudate. Such being the case, one cannot expect any bactericidal action to occur in the exudate proper. It must be borne in mind, however, that such antiseptic oils as metaphen in oil (1:25,000) or merthiolate in oil (1:10,000) or caprokol in oil (1:2,500) come in contact with the infected pleural surfaces and sterilize the pleura.

Our studies of effusion in the Collapse Therapy Clinic of the Chicago Municipal Tuberculosis Sanitarium have shown us that the majority of effusions during the course of artificial-pneumothorax collapse are tuberculous in origin. In over 80 per cent of the patients with effusion we were able to demonstrate tubercle bacilli by smear, culture, or guinea-pig inoculation. In some cases, even when the sputum was negative, we found tubercle bacilli in pleural exudate.

We can safely assume, therefore, that medicated oils, when used, keep the oil bacteriostatic or even bactericidal in addition to allowing the infected pleura to come in contact with the antiseptic.

In the series of experiments with medicated oils we used gomenol, oil of cajeput, caprokol, merthiolate, and metaphen. Gomenol was used in a concentration of 5 per cent, and was found to cause quite a severe irritation of the pleura. Oil of cajeput was also found to be irritating. Metaphen in oil proved satisfactory with as low a concentration as 1:40,000. In one dog it caused a haemorrhagic nephritis when used in a concentration of 1:1,000. No doubt this was due to poisoning from the mercury present in the metaphen. Clinically, we found metaphen in oil in a concentration of 1:25,000 to be nontoxic and satisfactory antiseptic. Birkhaug (38) reports a disinfecting effect on staphylococci with an aqueous solution of 1:140,000 of metaphen and a disinfecting effect on *Streptococcus haemolyticus* in concentration of 1:90,000. Caprokol was used in a concentration of 1:5,000 with good results.

In order to determine the bactericidal action of various antiseptics

we injected into the pleura varying amounts of positive sputum obtained from patients. These injections were made on dogs with eleothorax induced with metaphen, merthiolate, or caprokol. We found that a massive pleurisy resulted in the dogs in whom no antiseptic was used and in the dogs that received gomenol. On the other hand, the dogs with antiseptic oil tolerated the sputum. Examination of the samples of oil at varying intervals showed live organisms, but apparently their virulence must have been diminished by the contact with the medicated oil.

Others who have carried out work with this viewpoint in mind report similar results. For instance, Tullock and Ross (39) in 1927 found that eleothorax with olive oil of low acidity is lethal for tubercle bacilli *in vitro* after exposure of the organisms for 24 hours at 37°C. They report that the glycerides and sodium salts of oleic acid exert a markedly lethal action on the tubercle bacilli. This is not exerted on other organisms. They also found that mineral oil has not proven lethal for tubercle bacilli after exposures of nine days. P. Kellos (40) in 1932 noticed a peculiar granular formation of the tubercle bacilli and a change in the form of the organism after exposure to the oil. They became long and thread-like. He found that these organisms were virulent on guinea-pig inoculation.

We were anxious to find the relative sensitivity of the pleura and the peritoneum. Knowing that the peritoneum and the pleura are morphologically related (41) and their function similar, we repeated the experiments of Glimm, Peiser, Hirsche, Vignard and others. Our results were quite enlightening, because we found that oils, both plain and medicated, are well tolerated by the peritoneum. No symptoms developed in any of the animals except in one, in which the stomach-wall was injured during the injection and a peritonitis which developed proved fatal in 24 hours. In the others the oil remained unchanged or was emulsified. No additional exudate was noticed. The peritoneal surfaces of the viscera showed an oily film over them but no evidence of inflammatory reaction was noticed. With the exception of a possible adhesion at the site of the injection no adhesions were found in any of the animals. Except for the one that developed peritonitis, all the animals in this series were killed after an interval of 4 to 8 weeks.

In order to determine the mode of absorption of the oils from the pleural cavity, we injected into the pleura plain olive oil tinted with Sudan-III. This dye, being soluble in oil even in minute quantities, makes a very satisfactory dye for such a purpose. Furthermore, it proved nontoxic

as has been determined by Zieman (42), who injected large quantities of this dye into the dogs without any complications. To avoid fat embolism Zieman injected intravenously as much as 100 cc. of 20 per cent Sudan-III in alcohol after a good drunken state was produced; the animal recovered very promptly. Zieman finds that this dye is taken up by the endothelial system and excreted through the liver within a few minutes after the injection. Intrapleural injections of Sudan-III in oil show that the dye penetrates into the deeper layers of the pleura and is taken up by the lymphatics to reach the hilar lymph nodes. From there it is taken through the thoracic duct into the circulation and is found in the liver. Evidently, the oil follows a similar course.

In one experiment we injected merthiolate ointment into the chest cavity. This was prepared for us by the Eli Lilly Co. through the kindness of Dr. Homer H. Marks of the Medical Research Department. This ointment was made up of lanolin 10 parts, ceresin 5 parts and petrolatum 85 parts. This combination, though not irritating to the pleura, did not produce a satisfactory collapse. It may be possible that such a combination may prove of value in cases of extrapleural pneumolysis when a non-irritating pack of soft consistency may be desired.

Our experiments on fat embolism have been discussed under that heading. Suffice to say that fat embolism is just as serious a complication in eleothorax as air embolism is in pneumothorax. Precautions in the technique of injecting the oil will prevent this difficulty.

CHEMISTRY OF MATERIALS USED

Since the use of oils in eleothorax therapy involves some understanding of the chemistry of oils, we hope to give a brief résumé of the chemistry of fats. For those interested in a detailed study of the subject we suggest the use of the text of Lewkowitsch (44) and also of Cohen (45). The first accurate work on the chemistry of fats and oils was done by Chevreul (46). Oils are included among the liquid fats, and these in turn are divided into saturated and unsaturated. The fats are monoglycerides, diglycerides and triglycerides of saturated or unsaturated fatty acids. The general formula of fatty acids is $C_nH_{2n}O_2$. Fatty acids are characterized by the carboxyl group ($-C^{O}_{OH}$), the characteristic group of most organic acids. The three common acids found in fats of plant or animal origin are stearic acid ($C_{18}H_{36}O_2$), palmitic acid ($C_{16}H_{32}O_2$), and oleic acid ($C_{16}H_{34}O_2$). Oleic acid is an unsaturated fatty acid because it contains 2 atoms of hydrogen less than the stearic acid which is a saturated acid.

The glycerides, as they occur in fat, are known as *stearin*, *palmitin* and *olein*. The first two are solid at ordinary temperatures and pressures while olein is liquid. Other common glycerides are the butyric acid ($C_4H_8O_2$) and linoleic acid ($C_{18}H_{32}O_2$). A list of the more important glycerides are included below. This also includes the phosphatides and waxes. A list of various vegetable oils is also included.

Oils

I. Fats (*Liquid Fats, Fatty Oils, Solid Fats*)

1: Monoglycerides

a: Monoglycerides of fatty acids

1. Monoformin; 2. monoacetin; 3. monobutyrin; 4. monovalerin; 5. monolaurin; 6. monomyristin; 7. monopalmitin; 8. monostearin; 9. monoarachin; 10. monocerotin; 11. monomelissin.

b: Monoglycerides of unsaturated fatty acids

1. Monoölein; 2. monostearolin; 3. monobehenolin.

2: Diglycerides

a. Simple diglycerides

1. Diglycerides of saturated fatty acids

1. Digormin; 2. diacetin; 3. dibutyrin; 4. divalerin; 5. dilaurin; 6. dimyristin; 7. dipalmitin; 8. distearin; 9. diarachin; 10. dicerotin; 11. dimontanin; 12. dimelissin.

2. Diglycerides of unsaturated fatty acids

1. Diolein; 2. dierucin; 3. dibrassidin; 4. dilinolin; 5. distearolin; 6. dibehenolin.

b. Mixed diglycerides

1. Diglycerides of saturated acids

1. Lauromyristin; 2. laurosterin; 3. stearomyristin.

2. Diglycerides of unsaturated acids

1. Acetylstearolin; 2. Acetylricinstearolin.

3: Triglycerides

a. Simple triglycerides

1. Of fatty acids (saturated)

1. Triformin; 2. triacetin; 3. tributyrin; 4. trivalerin; 5. tricaproin; 6. tricaprylin; 7. tricaprin; 8. trilaurin; 9. trimyristin; 10. tripalmitin; 11. triheptadecylin; 12. tristearin; 13. triacachin; 14. tricerotin; 15. trimelissin.

2. Of unsaturated fatty acids ($C_nH_{2n} - {}_2O_3$), simple

1. Triolein; 2. trielaidin; 3. trierucin; 4. tribasidin; 5. tripetroselinin; 6. tristearolin.

3. Of trihydroxylated fatty acids ($C_nH_{2n} - {}_2O_3$)

1. Triricinolein; 2. triricinolaidin.

b. Mixed triglycerides

1. Mixed triglycerides containing acid radicles of saturated fatty acids only

1. Acetodiformin; 2. acetodibutyrin; 3. acetodilaurin; 4. acetodimyristin; 5. acetodipalmitin; 6. acetodistearin; 7. laurodimyristin; 8. myristodilaurin; 9. stearodilaurin; 10. laurotistearin; 11. laurostearomyristin; 12. myristodistearin; 13. palmitodistearin; 14. stearodipalmitin.

2. Mixed glycerides containing acid radicle of saturated fatty acids and of unsaturated fatty acids of the series ($C_2H_{2n} - {}_2O_2$)

1. Myristopalmito-olein; 2. oleodipalmitin; 3. oleopalmitostearin; 4. eleodistearin; 5. elaidodistearin; 6. dioleostearin.

3. Mixed triglycerides with acid radicle of saturated acids and unsaturated fatty acids of the series ($C_2H_{2n} - {}_4O_2$)

1. Linolodipalmitin; 2. linolodistearin.

4: Phospatides

a. Lecithin.

II. Pure Waxes (liquid waxes, solid waxes)

1. Cetylpalmitate; 2. octodecylpalmitate; 3. ceryl palmitate; 4. myricyl palmitate; 5. cetyl stearate; 6. ceryl cerotate; 7. cocceryl coccerotate; 8. chlolisteryl palmitate; 9. cholesteryl stearate; 10. isocholesteryl stearate; 11. cholesteryloleate; 12. cholesteryl cerotate; 13. melissyl melissate. *Examples of natural waxes:* 1. recovered grease; 2. wool wax (lanolin); 3. "distilled grease," 4. beeswax.

III. Vegetable oils

1. Drying oils: 1. perilla oil; 2. linseed oil—flaxseed oil; 3. N'Gart oil; 4. tung oil—Chinese tung oil, Japanese tung oil; 5. Lallemantia oil; 6. candle nut oil; 7. Stillingia oil—tallow-seed oil; 8. white acacia oil; 9. garden rocket oil—Dame's violet oil; 10. hemp-seed oil; 12. burdock oil—bur oil; 13. gynocardia oil; 14. Manketti oil—Nsa-Sana oil; 15. walnut oil—nut oil; 16. arbut-seed oil—arbutus unedo oil; 17. Linaria oil; 18. safflower oil—saffron oil; 19. Kaya oil; 20. Inukaya oil (Bébé oil); 21. Echinops oil (thistle-seed oil); 22. soja-bean oil (soy-bean oil, bean oil, Chinese bean oil); 23. Poppy-seed oil; 24. asparagus-seed oil; 25. Amoora oil; 26. Manihot oil (Ceara rubber-seed oil); 27. Funtumia oil; 28. Para rubber-tree-seed oil (rubber-seed oil); 29. Melia azedarach oil; 30. Croton Elliot-Ames oil; 31. henbane-seed oil; 32. millet-seed oil; 33. Niger-seed oil; 34. sunflower oil; 35. yellow acacia oil; 36. service-berry oil (mountain-ash-berry oil);

37. Celosia oil; 38. Argemone oil; 39. fir-seed oil; 40. dodder oil (meline oil); 41. wallflower-seed oil; 42. Madia oil.

2. Among the lesser known drying oils Lewkowitsch mentions: 1. Strawberry-seed oil; 2. raspberry-seed oil; 3. red currant-seed oil; 4. cranberry-seed oil; 5. hop-seed oil; 6. bilberry-seed oil; 7. hawthorne-seed oil; 8. blackberry-seed oil; 9. mulberry-seed oil; 10. Weld-seed oil; 11. Isano (Ungueko) oil; 12. Mohamba oil.

3. The semidrying oils are: (The cotton-seed-oil group): 1. Celandine oil (swallow-wort oil); 2. Daphne oil; 3. clover oil (red clover oil, white clover oil); 4. pumpkin-seed oil; 5. colcynth oil; 6. Ikpan-seed oil; 7. Narras-seed oil; 8. Bryony oil; 9. watermelon oil; 10. Senat-seed oil; 11. maize oil; corn oil; 12. tomato-seed oil; 13. persimmon-seed oil; 14. wheat oil; 15. Datura oil; 16. beechnut oil; 17. kapok oil; 18. cotton-seed oil; 19. sesame oil, beniseed oil, gingelli oil, teel oil; 20. basswood oil; 21. lemon-pips oil; 22. Luffa-seed oil; Loofah-seed oil; 23. myrtle-seed oil; 24. pecan oil; 25. spindle-tree oil; 26. Anise-seed oil; 27. croton-oil; 28. Zachun oil; 29. Carcas oil, purging-nut oil, physic-nut oil; 30. Brazil-nut oil; 31. Mucuna oil; 32. sorghum oil; 33. Coumou oil; Batavia oil; 34. pinot oil, para-palm oil, para butter.

4. Lesser-known semidrying oils are: 35. Laburnum-seed oil; 36. apple-seed oil; 37. pear-seed oil; 38. ash-seed oil; 39. Hure-seed oil; 40. small fennel-seed oil; 41. Indian-laurel-seed oil; 42. tobacco-seed oil; 43. orange-seed oil; 44. Casso-seed oil; 45. Chinese staranis-seed oil; 46. Japanese staranis-seed oil; 47. barley-seed oil; 48. Bonduc-nut oil; 49. nicker-seed oil; 50. coriander-seed oil; 51. tamarind-seed oil; 52. fern oil; 53. paprika oil; 54. bean oil; 55. rye-seed oil; 56. linden-tree oil; 57. spindle-tree oil; 58. larkspur oils.

5. The rape-oil group includes: 1. Garden-cress oil; 2. ravison oil; 3. rape oil (Colza oil); 4. black mustard-seed oil; 5. white mustard-seed oil; 6. radish-seed oil; 7. Jamba oil.

6. The lesser-known oils from Cruciferae are: 1. Water-cress oil; 2. winter-cress oil; 3. sea-kale oil; 4. spoonwort oil; 5. hedge mustard oil; 6. woad oil.

7. Among the nondrying oils Lewkowitsch includes: 1. Quince oil; 2. cherry-kernel oil; 3. cherry laurel oil; 4. apricot-kernel oil; 5. plum-kernel oil; 6. peach-kernel oil; 7. almond oil; 8. wheat-meal oil; 9. Sanguinella oil, dogwood oil, cornel oil; 10. acorn oil; 11. California nutmeg oil; 12. olive oil; 13. peanut oil, earth-nut oil, ground-nut oil; 14. rice oil; 15. Marsecan

olive oil; 16. tea-seed oil; 17. Tanbaki oil; 18. pistachio oil; 19. hazel-nut oil; 20. elderberry oil; 21. staff-tree oil; 22. olive-kernel oil; 23. callophyllyn oil; 24. coffee-berry oil; 25. strophanthus-seed oil; 26. senega-root oil; 27. cycopodium oil; 28. paradise-nut oil; 29. secale oil; 30. oil of Java olives.

Fatty oils or liquid fats are recognized as drying, semidrying, and nondrying oils. This classification is based on the degree of oxygen absorption by an oil when exposed to the air. The final product resulting from oxidation of a drying oil is varnish. This principle is used in painting.

Another important differentiation is that of oils and fats on the one hand, and the waxes on the other. The fixed oils and fats consist essentially of glycerides, that is, esters formed by the union of three molecules of fatty acids with one molecule of the trihydric alcohol, namely, glycerine. The waxes consist of esters formed by the union of one molecule of fatty acid with one molecule of a monohydric alcohol, such as cetyl alcohol ($C_{16}H_{31}OH$) or cholesterol ($C_{26}H_{44}O$).

It is important to remember that oil is a mixture of at least two or three different glycerides, particularly stearin, palmitin, and olein.

In order to determine the amount of fatty acid present in an oil the saponification value of an oil is of importance. In eleothorax therapy it is quite essential that as little free acid be present as possible. The saponification value represents the amount of alkali necessary to neutralize the fatty acids in a given oil or fat. It is estimated by heating a weighed amount of the substance with a standard solution of alcoholic potash an excess of which is taken. The fatty acids unite with the alkali and form the potassium salts. The excess of alkali, and, consequently, the quantity of alkali required for neutralization of the fatty acid is ascertained by titration with standard hydrochloric acid.

The iodine value or iodine number of a fat measures the degree of unsaturation of the oil sample. It represents the amount of iodine absorbed by the unsaturated fatty acids, thus forming additive compounds with iodine.

The melting and boiling points of fats are also of great importance in determining the degree of adulteration of oils used for eleothorax. The saponification number will show the amount of free fatty acids (degree of rancidity) present. The iodine number gives an idea of the presence of unsaturated oils.

The presence of semidrying oils, such as gomenol and oil of cajeput,

is important. These oils absorb oxygen from the tissues, and in time cause definite unsatisfactory reactions in the pleura resulting from contact with the oxidation products present. It is for this reason that we do not favor the use of gomenol or oil of cajeput. Nondrying saturated oils, on the other hand, except for changes due to hydrolysis, remain unchanged, particularly when protected from air and light. C. Friedel (47) has found unchanged triglycerides in the fat which has been buried several thousand years ago in the tombs of Abydos.

Liquid paraffin or mineral oil is used by many doing eleothorax work. This substance is not a true fat. It belongs to the class of saturated hydrocarbons, the simplest compound in this class of being methane (CH_4) which is found in marsh gas $({}_3CH_4)_n$. It is obtained by fractional distillation of earth or rock-oil. Naphtha, gasolene, kerosene, paraffin, wax, tar, and from the tar a long line of dyes, are the various products obtained from the rock-oil.

Paraffins are indifferent to most reagents and particularly oxidizing agents. Chlorine and bromine, but not iodine, combine directly with paraffins, and the action is promoted by light. When chlorine or bromine unites with the hydrocarbon, the alkyl chlorides or bromides are formed with the liberation of free hydrochloric acid. These substances are close chemical relatives of common chloroform group. They are quite toxic.

It is for this reason that we object to the use of paraffins in eleothorax. If the paraffin droplets enter the circulation and reach various organs, they cannot be oxidized readily. They are bound, therefore, to act as foreign bodies or else unite with chlorine to form halides which are toxic. Olive oil when absorbed is either hydrolyzed or oxidized, so that no after effects are to be expected.

A brief discussion of the chemistry of the antiseptics used may prove valuable. Metaphen, Birkhaug (38) states, is a 4-nitro-3, 5-B isacetoxy-mercuri-2-cresol. It is heavy yellow powder insoluble in water, soluble (1:500) in dilute aqueous sodium hydroxide (pH 9.0); in which it assumes a brownish red color in high concentration, and an amber color in low concentrations. It is soluble in 95 per cent alcohol. It contains 59.98 per cent of mercury. It is easily tolerated by white rats when 4 mgm. per kg. is given intravenously or 30 mgm. per kg. intramuscularly. A dilution of 1:20,400,000 inhibited growth of staphylococcus aureus in 24 hours. Dr. Biehn states that metaphen in oil (1:1000) may be heated to 100°C., if necessary, without any appreciable changes in the chemical.

He further states that metaphen is not soluble in liquid paraffin. For further details about its properties, we suggest that Birkhaug's original article be consulted.

Gomenol (niaouli oil) is described by Ray Matson (18) as a volatile oil, colorless or slightly yellow, aromatic, and obtained by distillation of the leaves of *Melalenoa viriflora*, belonging to the family of myrtle trees, growing abundantly in the region of Gomen, New Calendonia, from which the name of the product is derived. Gomenol resembles oil of cajeput in its properties and composition. Matson states that the oil has been reported as being nontoxic, and quotes Clerk as saying that gomenol inhibits the growth of bacteria in vitro and in vivo. Clerk states that "The acid fast organisms were killed in from five minutes to three hours, whereas it required from 3 to 9 hours to kill the staphylococcus." On the basis of these findings, Matson advises the use of 4 to 5 per cent for tuberculous empyema and 5 to 10 per cent in mixed infections.

SUMMARY

1. In a historical review of the subject we find that eleotherapy was used even by the ancients. Reference is made of this treatment by the Evangelist Luke.

2. The injection of oil for collapsing the lung in tuberculosis has been gradually developed and was first preformed by Matson and Mackenzie of Portland, Oregon, in 1914.

3. Bernou in 1922 coined the word *oleothorax*. Because this term is not etymologically correct, we suggest the use of the term *eleothorax* (*elaiothorax*).

4. The indications, contraindications, results, technique, and the chemistry of oils have been discussed in detail.

5. No report of our clinical cases is made because our clinical data are no different than those given in previous articles.

6. Emphasis is made of the danger of fat embolism during the course of eleothorax therapy. This complication has been completely neglected and has been mentioned before only in connection with accidents. An attempt has been made to give details for its diagnosis and prevention.

7. We believe that eleothorax should be given its proper recognition in collapse therapy of pulmonary tuberculosis, because it has certain advantages over other types of collapse in the cases in which it is indicated.

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MANOMETRIC READINGS OF INTRAPLEURAL PRESSURES IN ARTIFICIAL PNEUMOTHORAX

A Discussion of Principles and Factors Involved, with a Plea for Uniform Methods of Reading and Recording Intrapleural Pressures[1]

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INTRODUCTION

The introduction and use of the manometer in connection with the therapeutic administration of pneumothorax are attributed to Saugman, of Vejlefjord, Denmark, dating back to 1904 according to Riviere (1), and to 1906 according to Balboni's recent historical review (2). Saugman (3) himself, in a German publication in 1908, refers to his addition of a water manometer to Forlanini's original apparatus, connected with the cannula used for puncture, and Riviere states that the manometer "was eschewed by Forlanini himself till as late as the year 1910." At any rate, Saugman appears to have been the first to realize the essential importance of the manometer, and it is fairly certain that other earlier workers in this field, including Murphy and Lemke, of Chicago, at first used no manometer. It is now recognized generally as being, as King and Mills aptly put it (4), the key to the whole situation. It is the most essential and important part of the whole apparatus, without which one is practically working blindly, and it soon became an integral part of all types of pneumothorax apparatus. While the simple U-type of water manometer has been most in favor, details of construction have varied, as well as methods of recording the pressures. Saugman thought that the water manometer used should measure up to 50 cm. of water pressure, beyond which a mercury manometer might be used; yet one of the most widely sold American models has a scale limited to about 12.5 cm. direct (in one limb, above 0) or about 25 cm. corrected (reading the difference in levels in the two limbs). Spengler, who was associated with Brauer, employed a double manometer, with both a mercury and a water column. Forlanini (5) in 1911 described a rather complicated double manometer,

[1] Based on *Studies and Recommendations of the Commitee on Artificial Pneumothorax of the American Sanatorium Association*, 1934 and 1935.

one part of which was arranged so as to record when the gas-cylinder cock was shut off, the other or "inner manometer" consisting of a single tube with a bulbous expansion apparently recording the pressures when the cock to the gas cylinder was open and the gas free to enter the needle. This idea was further elaborated by Parry Morgan (6) in England later on, and also Woodcock. Küss (7) employed his double-flask system itself as a sort of large-scale manometer as far as one can determine. He believed the patient should aspirate the gas by his own respiratory movements. Hamman and Sloan (8) used a modification of Brauer's apparatus with a double manometer (water and mercury) on a fairly large scale, as did Begtrup-Hansen. Single manometers are, however, the rule.

Other types of manometers than those cited above, which have been used in connection with pneumothorax apparatus, are the anaeroid, not uncommonly employed where it is desired to reduce the total bulk of the apparatus, as in those designed by Mainini and by Heaf, in England, but admittedly lacking the accuracy and sensitiveness of the mobile fluid manometer; also, those in which other fluids, such as bromoform and oil, are used instead of water or mercury.

The question of the proper kind of manometer and proper methods of reading and recording has come to the fore especially in the last few years, during which the practice of pneumothorax therapy has become much more widespread, and patients not infrequently come under the successive care of several institutions or operators. Under these circumstances the discrepancies and diversities in the reading and recording of intrapleural pressures became more manifest and disconcerting. If careful observation of the behavior of the manometer is important, as emphasized by numerous authorities, and in particular by Parfitt and Crombie (9), not only to determine the pleural space, but the amount and frequency of refills needed, the state of the mediastinum, and other details, how can we reconcile this with the chaos and confusion which too often exist in practice?

Howson (10), of Los Angeles, in a careful paper published in 1929, suggested that a committee of the National Tuberculosis Association consider the question of formulating an acceptable standard for reading and recording manometric pressures. At this time, the American Sanatorium Association had appointed, first as a subcommittee of its Clinical Research Committee, now defunct, a *Committee on Artificial Pneumothorax* which was at first occupied with other matters. However, the controversy between the advocates of the "direct" or single-arm method

of reading and those of the "true" or "corrected" method, which measures the difference between the fluid-levels in the two limbs of the manometer, became more noticeable; and in 1932 a paper appeared in THE AMERICAN REVIEW OF TUBERCULOSIS by Bacon (11), criticizing the latter method as having no warrant or sanction in custom, authority or the laws of physics or physiology. In June, 1933, the matter was formally brought to the attention of the American Sanatorium Association, which officially adopted a motion to refer it to the Committee on Artificial Pneumothorax for study and recommendations. Meanwhile, K. P. Jones (12) reported, in a paper published in 1934, that only 4 out of 30 "authorities on pneumothorax" in the United States, queried by questionnaire, stated that they corrected their manometric readings, 18 reading directly from a single arm and the others apparently being noncommittal on this point. The Committee, however, found the corrected method of reading (by doubling the extent of excursion in a single limb of the U-tube) to be in use at such well-known places as Trudeau Sanatorium and Loomis Sanatorium, Bellevue Hospital in New York City, Gaylor Farm Sanatorium, Wallingford, Connecticut, as well as at English sanatoria and institutions generally; and that several types of apparatus, both in the United States and England, and on the Continent of Europe had the graduated scale for the manometer marked in half-centimetres to facilitate reading directly the corrected figures. A definite report (13) and recommendations, after giving the subject careful consideration and study, and enlisting the services of a trained physicist, were presented and adopted by The American Sanatorium Association in June, 1935, and should lead to uniform methods and procedure. It is intended here to review and discuss more fully the basis and rationale of the recommendations then made.

HISTORY OF MANOMETERS IN PHYSIOLOGY

Having already sketched the development of the manometer in the history of pneumothorax therapy, we may now go further back and inquire concerning its first appearance and use in physiology and what methods of reading have been employed there.

We are not sure just how far back the use of manometers to record pressures of one kind or another goes. Howell (14) states that Dr. Stephen Hales in 1733 first measured the "static pressure of blood" in arteries and veins directly by tying the femoral artery of a horse to a 9-foot glass tube in which he noted that the blood-column mounted to a

height of 8 feet, 3 inches. Poiseuille, of Paris, is generally credited with the first application of the mercury manometer for a similar purpose in 1828. According to Howell, he used a U-tube, one limb of which was connected with the interior of the artery by appropriate tubing filled with liquid. On releasing this, the mercury column in the tube to which a clamp was attached, was displaced. According to Poiseuille, again quoting Howell,

the difference in height between the levels of the mercury in the two limbs. . . .gives the (blood) pressure. . . .usually expressed as equal to so many millimeters of mercury. By this expression it is meant that *the pressure within the artery is able to support a column of mercury that many millimeters in height* and by multiplying by 13.5 the pressure can be obtained in terms of a column of blood (or water). [The italics and parenthetical insertions are ours.]

Howell himself adds that, when using the T-tube type of manometer, with a side connection, "*it is necessary to multiply the distance between the base line and the record (point) by 2 because the recording apparatus measures only the rise of the mercury in one limb; there is, of course, an equal fall in the other limb.*" Also, MacLeod (15), who has been erroneously quoted by Bacon in support of the single-arm method of reading manometers, says: "*The mean pressure is then equal to this distance* (height of the column above the zero mark) *multiplied by 2, because the distance through which the mercury has moved up in the manometer. . . is only one-half of the total displacement.*"

The same principles obviously apply whether we are measuring the pressure of blood in an artery or of gas in the pleural space (or in the potential space between the pleural layers before a pneumothorax has been induced) or the atmosphere of the earth, as in the case of the ordinary barometer. In the last instance, the fact that atmospheric pressure is being measured by the height of the column of mercury supported is obvious. It is almost equally so in the measurement of the blood-pressure in the brachial artery by the Riva-Rocci type of sphygmomanometer. A further and more direct illustration of measurement of pressure by height of column of fluid supported is found in the apparatus most commonly in use to determine the pressure of cerebrospinal fluid, which is simply a jointed glass tubing attached directly to the lumbar puncture needle by means of a right-angled joint, so that the tubing is set up in the vertical position and the height to which the fluid rises in it is

read directly as the actual pressure that this fluid is under. To state that the "distance travelled by the head of the column of fluid" is the real unit of measurement of pressures is to confuse matters and to set up arbitrary criteria and interpretations quite different from those which have been used and accepted by physicists and physiologists.

PHYSICAL PRINCIPLES OF MANOMETERS TO DETERMINE PRESSURES

Pressure is defined as *force per unit area* and is generally expressed in dynes or grams per square centimetre in the metric system of units or as pounds per square inch in the English system. Also, other ways of expressing pressure may be agreed upon and come into very general use. Thus, one usually expresses barometric pressure in terms of the height of a mercury column, in centimetres or inches, which the pressure of the atmosphere will support. Pressure involves both force and area though in certain cases it is not necessary to measure area directly. Thus, in the case of the mercury column the total force in grams is given by the height of column in centimetres times the density of mercury in grams per cubic centimetre times the area of cross-section. Then pressure in grams, which is total force divided by area of cross-section, is numerically equal to the height of column times the density of mercury.

Pressure differences may also be expressed in terms of the height of a mercury column and by attaching a U-tube manometer containing mercury to a partially evacuated vessel, the mercury will rise in the branch attached to the vessel, thus indicating a pressure less than atmospheric, or in the distal arm, indicating a higher pressure than atmospheric. When pressure differences to be measured are small, a less dense liquid than mercury is convenient and then water is generally used. In the case of intrathoracic pressures, the intrapleural pressure differs from atmospheric by only a few millimetres of mercury; therefore, it is usually more satisfactory to use a water manometer, since it is more accurate to read differences in heights of columns in centimetres rather than in millimetres and the lighter water column responds more readily to slight pressure changes. In this, as in similar instances, the linear factor, the principal variable, is conveniently used to express pressure instead of the compound unit referred to above.

The use of a manometer for measuring intrathoracic pressures really involves three distinct pieces of apparatus: (1) the manometer itself, (2) the needle through the chest-wall, and (3) the tube connecting the

manometer to the needle. When the needle connected to the manometer is passed through the chest-wall and the stylet withdrawn, the manometer, connecting tubing, and pleural cavity form a closed system, in which there is a periodical flow of air through the needle, equilibrium presumably being established at each expiration and inspiration between the air in the manometer and tubing on the one hand and the air in the pleural cavity on the other.

The pressure on each surface of the liquid in the manometer tube is equal to atmospheric pressure before beginning the measurement. Since the intrathoracic pressure is generally less than atmospheric, when the manometer is connected through the needle to the pleural cavity, there is a decrease in volume of the air between the manometer liquid and the aspirating needle, due to flow of air into the chest. The amount of this flow depends upon the pressure difference and also upon the volume of air in the connecting tubing. If the temperature is assumed to be constant, we may apply Boyle's law, which gives the relation between pressure and volume. This law may be stated as $PV = \text{const.}$, where P is the pressure and V the volume of the gas. For a small change in pressure the change in volume is given by $\Delta V = -\frac{V}{P}\Delta P$. Thus, *for a given pressure difference, the volume to be aspirated is greater, the larger the volume of air contained in the manometer arm and the connecting tubing.* A numerical example will illustrate this fact. Suppose the manometer arm and connecting tubing are 4 mm. in diameter and the tubing itself 120 cm. long. Then for a final pressure difference of 10 cm. of water at approximately atmospheric pressure, 0.7 cc. of air passes through the needle in order to establish equilibrium. If the manometer and connecting tubing have a diameter of 8 mm. and the same length as before (120 cm.), the amount of gas which must flow through the needle in order to establish equilibrium is 3.1 cc. Each of these calculations includes the air displaced by the rise of the liquid in the manometer tube. It is evident then that *in order to have as little total flow as possible* for a given pressure difference, *the volume of the connecting tubing and manometer should be as small as practicable.*

Now the question arises as to how the *length and diameter of the needle* affect the rate of flow of gas and consequently the reading of the manometer. It is obvious that, if the rate of flow through the needle is very small and the total flow necessary is large, equilibrium will not be reached either on inspiration or expiration and the pressure difference, as meas-

ured by the manometer, will be smaller than the real difference. As a limiting case, of course, the needle may be completely obstructed, in which case the pressure difference as read by the manometer is zero.

The needle is of small diameter and so the results arrived at for rate of flow of a gas through a capillary are applicable to this problem.

The rate of flow of air in cubic centimetres per second through a capillary is given by

$$V = \frac{\pi D^4}{128 Nl}\left(1 + \frac{3\zeta}{D}\right)\Delta P$$

where V is the rate of flow in cubic centimetres per second, D is the diameter of the capillary and 1 is its length. η is the coefficient of viscosity and ζ of the "slip coefficient." ζ becomes important only at pressures of the order of 1 mm. of mercury or less and so for the present purpose may be considered as zero. ΔP is the difference in pressure at the two ends of the capillary tube. This difference in pressure must be expressed in dynes per square centimeter since the coefficient of viscosity, η, involves pressure which is expressed in this unit.

Suppose one assumes a capillary tube 1 mm. in diameter and 5 cm. long. then D = 0.1 and 1 = 5. Assume also ΔP = 10 mm. of mercury which is about 14 cm. of water and is not unreasonably large.

N for air at 20° C. is 1808×10^{-7}

Then

$$V = \frac{\pi(0.1)^4 \times 1 \times 13.6 \times 980}{128 \times 1808 \times 10^{-7} \times 5} = 36.2$$

Thus, the maximum rate of flow is 36.2 cc. of air per second. Actually, of course, the pressure tends to equalize on the two ends of the needle and, if this equalization occurs in one second, the gas-flow is really only 18.1 cc. since ΔP becomes zero at the end of one second and the rate drops to zero. This latter calculation assumes the pressure difference varied linearly with time.

Now, suppose one uses a needle of only one-half the diameter, that is, 0.5 mm., all other conditions being equal. *Since the diameter enters as the fourth power, halving the diameter means that the rate of flow is only 1/16 as much* or the maximum rate of flow is only 2.3 cc. per second. The pressure difference, ΔP, continually decreases during expiration or inspiration, so that the volume of gas transpired in one second is less than

2.3 cc. *It is seen that the diameter of the needle has a very marked effect on the amount of air which will pass in a given time.* The length of needle is not quite so important since it varies only as the first power. Thus, a needle twice as long gives a rate one-half as great.

It is seen that with a very fine needle the rate of flow may be so small that equilibrium cannot be established at either inspiration or expiration and so the pressure *difference* as read on the manometer would be too small. How much the manometer readings differ from the actual intrathoracic pressure depends on the volume of gas to be transpired and, *the greater the volume of gas in the manometer and connecting tubing, the greater will be the departure of the manometer readings from the correct value.* The ideal arrangement then would be a very large needle with the manometer connected directly to the needle and the manometer tubing as small as is feasible. However, the manometer tubing should not be less than about 3 mm. in diameter, as otherwise the capillary force may cause the water column to break.

CLINICAL APPLICATION IN PNEUMOTHORAX APPARATUS

Thus, if we are to obtain reasonable uniformity in manometric readings, there must first be general agreement as to the type of manometer to be used, its bore or calibre and general principles of construction, and especially as to the manometer fluid. These are factors intrinsic in the manometer itself, but we have demonstrated that related extrinsic factors have an important effect on manometer readings, namely, length and calibre of the connecting tubing, type and calibre of needle, and other parts of the circuit, including the two-way stopcock in common use.

The water manometer has been in most general use nearly everywhere in the practice of pneumothorax and seems generally acknowledged as the best adapted for ordinary use. The employment of fluids of different viscosities, specific gravities, and other properties or of mixtures of these, introduces confusing and sometimes incalculable variables, the disadvantages of which overbalance the possible advantages. An exception may be made in the case of mercury, which may be used in a separate manometer circuit when very high or very low pressures are to be recorded. Practically, such necessity should seldom arise if the water manometer is of sufficient length and if some protective device is added against spilling over: as perhaps following an accidental cough or unusually deep inspiration, which tends to suck the manometer fluid into

the connecting tubing leading toward the needle. Some of the most widely known American apparatus, however, do not have manometers of sufficient length. Assuming the use of the U-tube type of manometer, its height above and below the zero mark should certainly be 15 and possibly 20 cm. It could be manufactured with a water-tight folding joint, if necessary, to fit into a case of convenient size. The marking of the graduated scales has been improved and made better visible in recent years, but some coloring matter added to the water in the manometer, such as fuchsin or mercurochrome, is usually advantageous. Marking the graduated scales in half-centimetres, in order to facilitate the direct reading of the correct pressure, is probably more reliable than depending upon the operator to correct his own readings by doubling them. The necessity of such correction is now recognized by such standard text-books as Riviere (1), Lilienthal (16), Davies (17), Dumarest and Brette (18), and in such excellent discussions as those of Sewall (19), Howson (10) and Bunta (20). The consensus of opinion of these authorities, together with the *Pneumothorax Committee Report* (13) mentioned above, should dispose of further controversy on this point.

The question of the *reliability of manometric readings*, granted that a uniform method of reading and a standard type of apparatus be employed, is often raised. We have attempted to explain and calculate the effects of various mechanical and physical factors, all relating to the manometer or some other part of the circuit between it and the pleural space. *The influence of the length and diameter of the connecting tubing* are often overlooked, although their importance has been mathematically demonstrated and can readily be verified clinically. *The rôle of the pneumothorax needle* itself is rather more obvious. Too fine a needle will always result in hindering satisfactory manometric excursions, and its lumen is readily obstructed either by a small quantity of fluid (from water in the sterilizer if boiled or from anaesthetizing fluid if a syringe has been attached) or a tiny bit of tissue. For practical purposes, a needle smaller than 20-gauge Luer (about 0.8 mm.) is undesirable, while one larger than 17-gauge (about 1.2 mm.) becomes too traumatizing and increases the likelihood of escape of air into the subcutaneous tissues. The question of bevel and of side-opening or use of the stylet need not be taken up as not directly bearing on the question of manometric readings.

The effect of the bore or calibre of the manometer tube itself has already been discussed, and can readily be tested by the operator. Two of the best known makes of apparatus in our Eastern United States have in-

ternal bores of manometer varying from 3 to 7 mm. This difference will result in widely different excursions, as pointed out by Riviere (1), Saugman (21), Howson (10), and others. The smaller manometer tube is more sensitive, and its excursions more prompt and ample. Too great a lag and inadequate respiratory excursion result with the larger tube. On the other hand, Bucher (22) has pointed out that with the use of manometer tubing under 2 mm. diameter (internal bore) the continuity of the column is apt to be interrupted. This is explainable on the grounds of surface tension and capillary attraction. Howson, in his experiments, found the inspiratory readings, especially negative pressures, most affected by the difference in manometer bore and this is especially important if the readings at the height of inspiration are taken as the record point, as advocated by Bunta. We think it preferable to record both inspiratory and expiratory pressures with the patient breathing normally.

FACTORS INTRINSIC TO THE PATIENT

These have been studied to some extent by a number of workers among whom we may mention Parfitt and Crombie, Sewall, and Bunta (already cited). Some of these factors most definitely affecting the intrapleural pressures and the manometric readings are:

1. Position of the patient
2. Respiratory movements—amplitude, rapidity, regularity
3. Condition of the mediastinum
4. Presence of exudate in the pleural cavity
5. Condition of the pleura (both visceral and parietal).

Position of the patient: The effect of different positions on the intrapleural pressures has been studied by several workers. The customary position for administration of air, with the patient lying on the opposite side, the intercostal spaces on the affected side being stretched apart by a small cushion or bolster under the dependent side of the thorax (not the hips or shoulders), usually affords the widest manometric respiratory excursions. Manometric readings should not be recorded until the patient is breathing evenly and regularly (except in initial insufflations, when there ordinarily occurs a succession of downward thrusts and one waits until these have reached the furthest point). If the patient is turned on his back the intrapleural pressures are higher, due to the abdominal viscera and the diaphragm rising and diminishing the size of the hemithorax.

Respiratory movements: Anything which affects the rate and depth of respiration will of course be reflected in the manometric readings. A dyspnoeic patient, provided respiratory movements are not restricted, will show larger excursions than one breathing quietly. Patients in whom shallow or intercostal respiratory movements predominate will show less satisfactory excursions than where the diaphragm actively participates. Emphysematous patients usually show abnormal excursions.

Condition of the mediastinum: The effects of differences in this factor have been so completely and ably discussed by Parfitt and Crombie (23) that there is little to add. A weak or flexible mediastinum results in a delayed rise in manometric readings, with little difference between inspiration and expiration. A rigid mediastinum produces opposite effects.

Presence of pleural exudate: This, by diminishing the size of the pleural space, results either in abnormally high initial pressures or abnormally rapid rise in the pressures. If there is much fluid depressing the diaphragm there may be absence of respiratory excursions.

Condition of the pleural membranes: Pachypleuritis ordinarily occurs eventually and gradually but, if there has been an exudate, the effects of fibrotic and fibrinous changes are more promptly manifest. As there is a general rigidity, the effect of the respiratory excursions is reflected in a marked rise and fall of the manometer fluid and the pressures rise more rapidly after insufflation than with a normal pleural lining. If the space is restricted by adhesions the rise in pressure is accelerated.' Conversely, if fluid has been absorbing and any considerable air space remains, the initial pressure may be abnormally low, because the encasement of the lung by a rigid visceral pleural layer prevents its expanding as it otherwise would to fill the surplus space. Hence, the "drawing sensations" that patients experience under these circumstances, are relieved by introducing air, which reduces the tension due to abnormally negative (subatmospheric) pressures between the lung and chest-wall.

DISCUSSION

On the basis of careful clinical observations and experience supplemented and supported by the mathematical computations cited in the consideration of the physical principles involved, the following standards and specifications have been suggested for general adoption in the construction of artificial pneumothorax apparatus, for the purpose of bringing

about greater uniformity and accuracy in practice and in recording intrapleural pressures:

1. For manometer and connecting tubing, a diameter of 3 to 5 mm., average 4 mm.

2. For pneumothorax needle, 17- to 20-gauge Luer (0.8 to 1.2 mm. diameter), average 18- or 19-gauge Luer, or about 1.0 mm. diameter, the needle to be 2 to 2.5 inches long.

3. Connecting tubing should be as short as feasible. Practical considerations require a sufficient length to extend from the outlet of the pneumothorax apparatus to the needle when inserted in the patient's chest.

SUMMARY AND CONCLUSIONS

In accordance with the physical principles already discussed and their clinical application, as herein set forth, certain recommendations for the standardization of artificial pneumothorax apparatus and for reading and recording manometric pressures have been made and accepted by the American Sanatorium Association. These have been discussed and summarized, and should be utilized by practitioners of pneumothorax therapy. The intelligent use of the manometer in pneumothorax practice is fully as important as that of the X-ray and fluoroscope.

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THE INFLUENCE OF ARTIFICAL PNEUMOTHORAX ON THE BACILLARY COUNT IN OPEN CASES OF PULMONARY TUBERCULOSIS[1]

EMIL BUNTA

From the public-health standpoint, the focus of attack in the campaign against tuberculosis is the positive sputum-carrier. The harmful effects attributed to the open pulmonary case in any community vary in proportion to the density of population, the number of such infected individuals, and the quantity of tubercle bacilli which they disseminate. Any method effecting a reduction of the bacillary mass, or, better still, an eradication of infectious organisms from the sputum of pulmonary cases is conducive to the prevention and control of tuberculosis.

One of the major accomplishments in the collapse treatment of pulmonary tuberculosis is sputum conversion. Of the various measures instrumental in suppressing tubercle bacilli from the sputum, artificial pneumothorax ranks as the method of choice. In a recent study, Bendove and Reiss (1) showed that, of all the cases which became negative after the initiation of pneumothorax, about 50 per cent do so within the first three months and 82 per cent within six months of treatment.

The nature of the bacillary changes antedating conversion in consequence of pneumothorax therapy is a problem for clinical investigation. There are no available reports in the literature on this subject. Tice and Hruby (2) advance the theory that "The positive sputum does not convert over night, that preceding the conversion there is a gradual decrease in the bacillary count, which has a public health significance . . . that the individual whose sputum is loaded with bacilli is more of a public health menace than the individual with meager sputum and only occasional bacilli."

The present study is concerned with the influence of artificial pneumothorax, in relation to time, on the bacillary count preceding conversion in positive-sputum cases of pulmonary tuberculosis, particularly those revealing unilateral cavitated lesions with and without complicating

[1] From the Collapse Therapy Clinic, Municipal Tuberculosis Sanitarium, Chicago, Illinois.

pleural adhesions on the collapsed side, and those showing bilateral pulmonary cavitation.

METHOD OF BACILLARY ESTIMATION

The material for study included 13,839 sputum reports in 506 pneumothorax-treated open cases of pulmonary tuberculosis; and 4,993 sputum reports in 642 officially registered open pulmonary cases not having had any form of collapse therapy. The latter group served as controls.

All the sputum work was done at the laboratory of Dr. Henry C. Sweany, Medical Director of Research, Municipal Tuberculosis Sanitarium. Each positive-sputum report in our series specified the number of bacilli, either "per slide" or "per field," the vast majority of which were submitted in terms of the latter. All counts, according to the former method, were embodied in the data as "less than 1 per field." This was done because the term "bacilli per slide" represents a lesser density of the bacillary mass than that implied in the term "bacilli per field." Àpropos the technique of bacillary estimation and significance of the readings of tubercle bacilli on the microscopic slide, Sweany (3) is quoted as saying:

> When we speak of bacilli per field, that, of course is self explanatory. Bacilli per slide has an entirely different meaning. That means the number of bacilli that are found on the slide in an approximate ten minute search. This actually represents about one tenth of a whole slide, therefore, ten bacilli per slide would actually mean about one hundred bacilli per slide. As there is about one fiftieth of a cubic centimeter of direct smear per slide and about one tenth of a cubic centimeter of concentration per slide, it means that there is from one thousand to five thousand per cubic centimeter of sputum. Supposing there are twenty cubic centimeters in twenty-four hours, that would make twenty to one hundred thousand bacilli expectorated in twenty-four hours. Take another example of two bacilli per field. As a result of some rather crude calculations, we have estimated that there are twenty thousand fields per slide. That makes forty thousand bacilli per slide, or four hundred thousand to two million per cubic centimeter. Should the patient have one hundred cubic centimeters of sputum, that would make one hundred times this quantity in twenty-four hours.

CLASSIFICATION OF PATIENTS

The nonpulmonary collapse or control group comprised 642 dispensary-supervised open cases of pulmonary tuberculosis ranging in age

from four to seventy-five years, the average for the group being 32.8 years. Of the total number of patients, 377, or 58.8 per cent, belonged to the white race; and 265, or 41.2 per cent, were Negroes. Male patients were in the majority with an incidence of 55.6 per cent. The group included 458 patients (71.3 per cent) with unilateral pulmonary cavitation; and 184 patients (28.7 per cent) with bilateral cavitation.

The pneumothorax-treated group consisted of 506 ambulatory tuberculous individuals, each of whom revealed a positive sputum when pneumothorax treatment was initiated. Their ages varied from twelve to sixty-three years, the average for the group being 28.8 years. From the racial point of view, the majority (74.1 per cent) were white; and the balance (25.9 per cent), colored. Males predominated in the series with an incidence of 53.4 per cent. The pneumothorax-treated patients were classified into three clinical groups. The first included 266 patients (52.6 per cent) with unilateral cavities confined to the treated lung, uncomplicated by pleural adhesions during the course of pneumothorax therapy. The second group consisted of 103 individuals (20.3 per cent) with bilateral pulmonary cavitation, only eight of whom underwent bilateral pneumothorax treatment. The third group comprised 137 patients (27.1 per cent) with strictly unilateral cavitated lesions complicated by pleural adhesions on the treated side.

STATISTICAL METHOD

The total number of sputa, including positive and negative, and the total number of bacilli per field for each successive three-month period dating from the first positive sputum were counted; and the average number of bacilli per field calculated for the respective time-intervals in both pneumothorax-treated and control patients. The data were then collected in the form of a scatter diagram and correlation table, using the three-month intervals ranging from three months or less to two years or more as the "x" variable or axis of abscissae; and the average bacillary count per field, ranging from 0, 0.1 to 10, 10.1 to 20, 20.1 to 30, 30.1 to 40, 40.1 to 50, 50.1 to 60, 60.1 to 70, 70.1 to 80, 80.1 to 90, 90.1 to 100, 100 plus, as the "y" variable or axis of ordinates in the diagram. A separate correlation table was made for the pneumothorax cases classified according to unilateral cavitation without pleural adhesions, bilateral cavitation, and unilateral cavitation with pleural adhesions; the total number of pneumothorax-treated individuals; and the total number of control patients. The Pearson correlation coeffi-

cient for each group was then computed in accordance with the method described by Thurstone (4). Finally, regression lines were drawn for the respective case-groups. The average bacillary count per field was calculated for each vertical column of the correlation table, and curves plotted connecting the averages.

RESULTS

A summary of the average bacillary count at varied intervals of time in pneumothorax treated and control patients appears in table 1. The findings contained in this table are graphically represented by regression lines in chart 1.

The nonpulmonary collapse or control patients averaged 7.8 bacilli per field, covering a period of more than two years dating from the

TABLE 1.

Summary of average bacillary count per field at successive intervals of time in pneumothorax-treated and noncollapse or control patients

CLINICAL GROUP	TIME INTERVALS IN MONTHS									AVERAGE TOTAL BACILLI PER FIELD
	3 or less	4–6	7–9	10–12	13–15	16–18	19–21	22–24	over 24	
Total noncollapse or control cases....	10.4	6.5	5.0	4.5	8.6	6.1	5.7	4.3	6.0	7.8
Total pneumothorax-treated cases....	12.2	8.4	6.1	5.3	4.9	4.8	3.3	3.8	5.1	7.3
Unilateral cavity cases without pleural adhesions.....	11.4	8.2	2.9	1.9	1.3	1.0	0.5	0.5	0.6	4.5
Bilateral cavity cases.....	10.3	11.9	10.9	10.5	11.9	14.1	8.4	13.1	13.6	12.1
Unilateral cavity cases with pleural adhesions.....	14.1	12.6	9.1	9.0	8.7	5.6	6.5	5.3	11.0	10.5

original positive sputum. During the first three months, the count averaged 10.4 bacilli, and in the closing period, 6.0 bacilli per field. The decline in the bacillary count was more direct prior to the 10-to-12-month interval than in subsequent months.

The general run of pneumothorax-treated patients averaged 7.3 bacilli per field over a period of more than twenty-four months, counting from the appearance of positive sputum and commencement of collapse therapy. In the first three months, the count averaged 12.2 bacilli, and in the final period, 5.1 bacilli per field. A progressive decrease in the bacillary count with increments of time was noted prior to the 19-to-21-month period.

In the nonadhesion pneumothorax cases with cavities limited to the

treated lung the average total number of bacilli over the entire period of observation was 4.5 bacilli per field. During the initial three-month interval, the count averaged 11.4 bacilli, and in the last period, 0.6 bacilli per field. A rather abrupt drop in the bacillary count and approximation to the conversion level occurred before the 7-to-9-month interval,

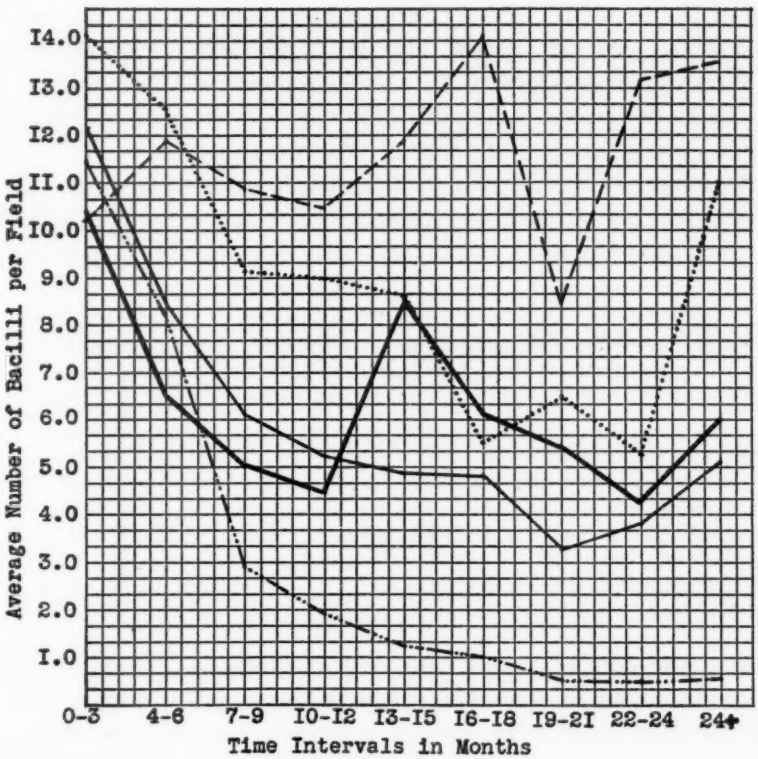

CHART 1. Regression lines showing the relation between the average bacillary count and time in pneumothorax-treated and nonpulmonary-collapse or control patients. Heavy unbroken line, control cases; light unbroken line, total pneumothorax treated cases; dots and dashes, unilateral cavity cases without pleural adhesions; broken line, bilateral cavity cases; dotted line, unilateral cavity cases with pleural adhesions.

followed by a relatively gradual diminishing count in the succeeding months of treatment.

The pneumothorax patients with complicating cavities in the contralateral or untreated lung averaged 12.1 bacilli per field covering the full period of observation. In the first three-month interval, the count

averaged 10.3 bacilli as against 13.6 bacilli per field in the concluding period. The general trend of the bacillary count in these cases was toward an increase rather than a decrease with the passage of time.

The pneumothorax-treated group with unilateral pulmonary cavitation and pleural adhesions affecting the collapsed lung averaged 10.5 bacilli per field over the entire period of observation. During the initial three-month interval, the count averaged 14.1 bacilli, and in the final or two-year-plus period, 11.0 bacilli per field. A step-like decrease in the average bacillary count with increments of time was noted prior to the 16-to-18-month interval, followed by a steep rise in the average count during the closing phase of treatment.

A summary of correlation coefficients expressed in terms of pure numbers indicating, in an objective and impartial manner, the relationship between the bacillary count and the time factor in pneumothorax

TABLE 2

Summary of correlation coefficients indicating the relationship between the bacillary count and the time factor in pneumothorax treated and noncollapse or control patients

CLINICAL GROUP	CORRELATION COEFFICIENT	
Total noncollapse or control cases		−0.13
Total pneumothorax-treated cases		−0.23
Unilateral cavity cases without pleural adhesions	−0.45	
Bilateral cavity cases	−0.02	
Unilateral cavity cases with pleural adhesions	−0.18	

treated and control patients is shown in table 2. The minus sign (−) before the numbers indicates a negative relationship, that is, a decreasing bacillary count with increasing intervals of time; and the number (not a per cent) indicates the degree of relationship. A perfect negative relationship would be expressed as −1.0. The numbers in the summary, therefore, represent comparative degrees of imperfect negative relationship between the time factor and the bacillary count.

SUMMARY OF RESULTS

In summation, it may be stated that a decrease in the bacillary count with increments of time was observed in both pneumothorax-treated and nonpulmonary-collapse or control patients.

Pneumothorax-treated patients in general revealed a more direct and sustained decrease in the number of tubercle bacilli and advancement

toward the conversion level with elapsing time, as compared to the control group.

All treated cases, except the group with bilateral pulmonary cavitation, revealed a more direct reduction in bacillary numbers prior to the 7-to-9-month interval than in the succeeding months of treatment.

From the standpoint of time, the most direct decrease in the bacillary count and earliest approximation to the conversion level was evidenced in nonpleural adhesion cases with cavities limited to the treated lung; and the least diminished count or approach to the conversion level in the pneumothorax cases with bilateral pulmonary cavitation. Pleural adhesions, on the other hand, exercised an inhibiting influence on bacillary reduction, though relatively less so than the cases with bilateral cavitation.

CONCLUSIONS

Preceding sputum conversion in open cases of pulmonary tuberculosis, pneumothorax therapy effects a progressive reduction of the bacillary mass in direct, though imperfect, relation to the length of treatment, the ratio depending on the presence or absence of pleural adhesions on the treated side, or cavitation in the contralateral or untreated lung.

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THE BLOCKED PULMONARY CAVITY

An Anatomical, Roentgenological and Clinical Study[1,2]

DAVID SALKIN, A. V. CADDEN AND R. B. McINDOE

The pulmonary cavity is playing an ever-increasing rôle in tuberculosis problems. Its indication of active disease and its dire effect upon prognosis have dominated the entire field of collapse therapy. Despite the tremendous literature on the subject the physiology of the cavity is still obscure. It is only in the last few years that the annular shadow has been regarded as cavity rather than pleural ring or localized pneumothorax. Some of the important unsolved problems are the exact methods of cavity healing, the cause of recurrence of healed cavities, the rapid changes in size of some cavities, and the lack of physical signs over many cavities. The cavity-wall is regarded as physiologically inert, but evidence is accumulating to show that it may be very active in determining the gaseous and liquid content and pressure within the cavity. There is even some doubt in our minds that a cavity is always formed by the ulceration of a tuberculous focus into the bronchial tree.

The purpose of this paper is to show that cavities may exist in the lung without any communication with the tracheobronchial tree and, in this state, may enlarge, absorb air or fluid and be productive of physical signs. In routine autopsy procedure it is very difficult to study the patency of bronchi leading to a cavity because of the distortion occasioned by postmortem manipulation and because of the long time necessary to trace all the many minute bronchi. For this reason, we have, in our autopsy material, outlined the tracheobronchial tree with a radio-opaque medium while the lungs were in normal position in the chest, and we have then confirmed the findings with autopsy. By this method of study we have been able to observe interesting phenomena dealing with alveolar filling, bronchial block, atelectasis, massive haemorrhage, bronchopleural fistula and the disposition of the bronchi

[1] From the Hopemont Sanitarium, Hopemont, West Virginia, and the Michigan State Sanatorium, Howell, Michigan.

[2] Presented at a session of the Clinical Section at the 32nd annual meeting of the National Tuberculosis Association, New Orleans, Louisiana, April 23, 1936.

under pulmonary collapse by pneumothorax and fluid. In this paper we shall deal only with cavities which do not communicate with the bronchial tree.

TECHNIQUE

In this study, immediately after the death of a patient the body was placed upright in a specially designed chair mounted on wheels, and was moved in front of an X-ray machine. The chair consists of a seat sloping downward and a high back containing a 14″ x 17″ casette holder. The exact time of the intrabronchial injection after death is of little importance, for similar results were obtained when the injection was made immediately after death or one hour later. Before injection a roentgenogram is made of the chest and the cadaver is then moved behind a fluoroscopic screen where the injection is made under direct vision. The dye may be introduced with a laryngeal cannula through the glottis, with a needle through the cricothyroid membrane; or a needle may be put into a cavity directly through the thoracic wall and the medium injected. The solution is introduced with only moderate speed as its course is followed upon the fluoroscopic screen.

Various opaque solutions have been used with equally good results: they include barium suspensions, potassium iodide, sodium bromide, hippuran, brominol and lipiodol. Our routine solution consists of a mixture of potassium iodide 10 gm., barium sulphate 20 gm., and milk 100 cc. This mixture produces a striking radiographic picture and the barium sulphate leaves a white coating on the walls of the cavities, alveoli and bronchi, which is easily traced during the dissection of the lung. The fluidity of this mixture is determined by occasional manual pressure upon the chest and observing the resultant changes of fluid-level in the bronchi and cavities. That the mixture is capable of traversing the finest bronchi is proved by the fact that it enters the alveoli, as seen on the fluoroscopic screen, X-ray film and dissection. When a cavity does not fill by bronchial injection, a needle is inserted into the cavity through the thoracic wall and the dye injected under fluoroscopic control. It is not necessary to change the position of the body for an upper-lobe filling. It is done as follows: The operator's hands are placed upon the anterior chest and firm pressure is directed downward and backward for a few seconds; then a quick release is made by removing the hands. By this method the air is first forced out of the upper lobe and the dye lying in the large bronchi is actually sucked up into the small bronchi and alveoli.

RESULTS

Our studies were begun October 24, 1933. Injections have been made in 70 cases in which death occurred from pulmonary tuberculosis. Of these, 33 cases had the injection alone and 37 cases also had autopsies.

TABLE 1

Blocked cavities: injection plus autopsy

NUMBER	NAME	DIAMETER IN CM.	LOBE INVOLVED	FLUID-LEVEL	CAVITY SIGNS	SIZE ANTEMORTEM	CAUSE OF BLOCK
1	P. A.	6 x 8	L. U.	0	+	Same	Extrabronchial fibrosis
2	A. P.	4 x 10	L. U.	0	+	Same	Extrabronchial fibrosis
3	J. H.	10 x 12	R. U.	+	Suggestive	Increased	Plug in bronchi
4	M. L.	8 x 12	R. U.	+	+	Increased	Inflammatory swelling
5	G. S.	4 x 6	R. L.	+	0	Increased	Inflammatory swelling
6	I. R.	4 x 5	R. U.	0	+	Same	Intracavitary
7	I. R.	4 x 5	R. U.	0	+	Same	Intracavitary
8	I. R.	3 x 5	L. U.	+	0	Same	Plug in bronchi
9	L. R.	3 x 5	L. U.	0	0	Same	Inflammatory swelling
10	H. G.	3 x 5	L. U.	0	+	Same	Inflammatory swelling
11	C. L.	3 x 3	L. L.	0	0	Same	Intracavitary
12	S. C.	4 x 6	R. U.	0	0	Increased	Inflammatory swelling
13	S. C.	4 x 5	L. U.	0	0	Increased	Inflammatory swelling
14	R. L.	4 x 4	R. M.	0	0	Varied	Plug in bronchi
15	O. P.	6 x 10	R. U.	0	0	Same	Inflammatory swelling

TABLE 2

Blocked cavities: injection alone

NUMBER	NAME	DIAMETER IN CM.	LOBE INVOLVED	FLUID-LEVEL	CAVITY SIGNS	SIZE ANTEMORTEM	CAUSE OF BLOCK
1	C. L.	6 x 10	L. U.	0	+	Increased	Unknown
2	M. H.	4 x 8	R. U.	0	0	Increased	Inflammatory swelling
3	H. G.	4 x 4	R. U.	+	+	Increased	Inflammatory swelling
4	A. I.	4 x 10	L. U.	0	+	Increased	Extrabronchial fibrosis
5	F. K.	3 x 4	R. U.	0	0	Decreased	Intrabronchial
6	J. K.	3 x 7	L. U.	0	0	Increased	Fibrosis of major bronchus

Only cavities of 3 cm. or more in diameter were studied, since the smaller ones presented many technical difficulties which made the results unreliable. Of the 70 cases, blocked cavities were noted in 18 (26 per cent). Of a total 147 cavities observed (over 3 cm. in diameter), 21 (14 per cent) did not communicate with bronchi. In the 18 cases with

21 blocked cavities there were also 28 ordinary cavities which did communicate with bronchi. Tables 1 and 2 list the noncommunicating cavities with regard to size, position, presence of a fluid-level, cause of the bronchial block, physical signs over the cavity immediately after death, and variation in size prior to death. When an autopsy was not done the possible factor in the blocking of the cavity is mentioned.

The causes of noncommunication of the cavity with the bronchial tree were found to be intracavitary, extrabronchial and intrabronchial. The intracavitary cause occurred in 3 cases; in these cases the cavities were filled so tightly with a fibrinogelatinous debris that the dye could not enter from the bronchi. (Figure 1.) The extrabronchial cause consisted of dense fibrosis and cicatrization incorporating the bronchi and cavity-wall; such a cause was found in 2 cases and must have existed for a long period of time. (Figure 2.) The intrabronchial causes were (a) obstructing plugs and (b) tuberculous bronchitis. Bronchial plugs were found in 3 cases and consisted of a tenacious mixture of pus, mucus and débris, which was firmly fixed in the bronchial lumen near the opening into the cavity and could not be dislodged by rough manipulation during the injection. (Figure 3.) The commonest cause was tuberculous bronchitis which was found in 7 cases. The bronchi showed marked mucosal swelling associated with petechiae in 2 cases; the oedema and hyperaemia were especially prominent in the smaller bronchi and gradually narrowed the lumen. Just at the border of the cavity the bronchi were entirely obstructed and became incorporated into the caseous wall of the cavity. These cases were typical of tuberculous bronchitis, which was manifested during life by severe paroxysms of cough. (Figure 4.) The walls of all these cavities, whether fibrous or caseous, showed gross and microscopic evidence of tuberculous activity with numerous areas of active destruction and reparation. (Figure 5.)

The size of the cavities under study varied from 3 cm. to 10 cm., and in 3 cases the cavity occupied an entire lobe. Nine blocked cavities were located in each right and left upper lobes; one each was found in the right middle, right lower and left lower lobes. A fluid-level was present in 6 cavities, the fluid consisting of liquefied and caseous débris. Serial X-ray studies prior to death showed that 10 cavities had increased in size (some very rapidly), 9 cavities had remained stationary for months, one cavity had decreased in size, and one cavity had shown rapid variations in size. The physical signs over these cavities were

recorded shortly before death, and in most cases on the day of death. Definite cavity signs were found in 9 cases; in two of these cases the cavities were found to be tightly filled with débris and did not contain air. The signs included definite bronchial or amphoric breath sounds, marked pectoriloquy, and coarse râles. Eleven cases presented no cavity signs and one case gave suggestive findings. With regard to size, it was noted that in the 12 cavities of 5 cm. or less in diameter, physical signs of cavity were positive in 4 cases, negative in 7 cases and suggestive in 1 case; while in the 9 cavities more than 5 cm. in diameter, positive signs were found in 5 cases, and no signs in 4 cases. In the 11 cases with no cavity signs, 7 cavities were deeply situated, 2 had an overlying pneumothorax, and 2 were overlaid with thick pleura.

Fig. 1. Intracavitary block shown by cavities at right apex completely filled with a fibrinogelatinous débris.

Fig. 2A. Extrabronchial fibrosis. Cavity at left apex is surrounded by dense fibrosis incorporating the bronchi and preventing filling of the cavity by the tracheal route.

Fig. 2B. Extrabronchial fibrosis about the left cavity and involving the major bronchi. This cavity was filled through the chest-wall.

Fig. 3. Intrabronchial plug. The cavity at the right apex was filled through the chest wall after its failure to fill by the tracheal method. The draining bronchus was tightly blocked with a pus plug.

Fig. 4A. Inflammatory occlusion. The cavity at right apex was filled through the chest-wall after its failure to fill by the tracheal method. All draining bronchi showed inflammatory block.

Fig. 4B. Inflammatory occlusion of the bronchi resulting in failure of the left apical cavity to fill by the tracheal method.

CLINICAL STUDIES

It is a common clinical experience to find that, shortly after the institution of pneumothorax or phrenic paralysis, all (or almost all) expectoration ceases but the cavity still persists. Cavities are sometimes seen in serial roentgenological studies as changing cyclically from an area of rarefaction to a dense shadow, and return to an area of rarefaction. We have seen several cases in which cavities have disappeared during pneumothorax and reappeared at the original site with a recurrence of positive sputum, but without a change in the size of the pneumothorax. A common explanation offered, is that the bronchi are kinked; injection of several pneumothorax lungs *in situ* has failed, however, to reveal intrabronchial or extrabronchial obstruction. Kinking of bronchi under pneumothorax is probably much rarer than is believed.

Fig. 3

Fig. 4A

Fig. 4B

Fig. 1

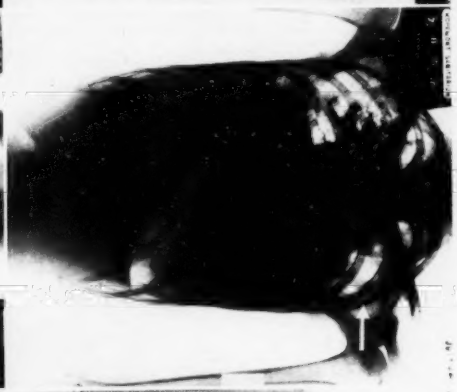

Fig. 2A

Fig. 2B

At the Hopemont Sanitarium we have been able to observe about 20 cases of clinically blocked cavities, of which the 15 most interesting will be described briefly in this article. Eight of the cases under study had no expectoration whatever at the time the cavities were believed to be blocked, despite the institution of postural drainage and administration of expectorant mixtures in all cases; the other 7 cases had mild expectoration. The listing of the sputum examination as negative means that

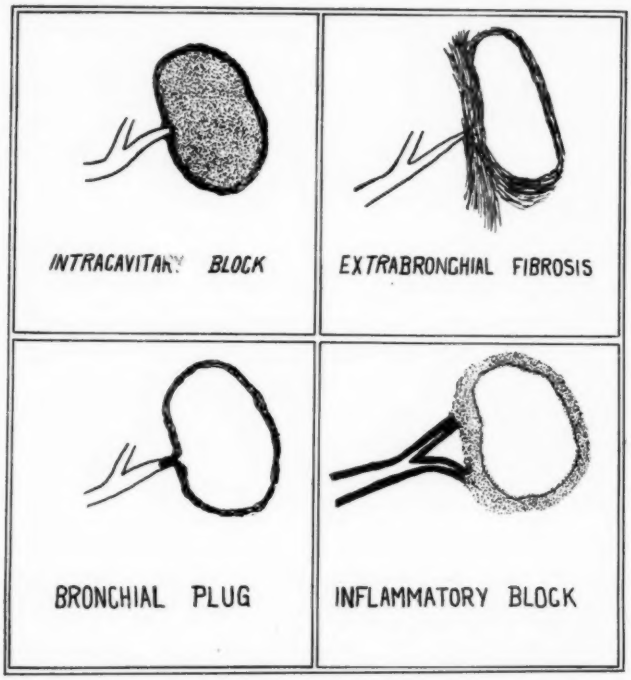

FIG. 5. DIAGRAM SHOWING THE FOUR CAUSES OF BLOCKED CAVITIES

there had been repeated plain and concentrated smears, cultures, and, in some cases, guinea-pig inoculations. In ten of the 15 cases to be described, the block was probably intrabronchial, and in two cases probably extrabronchial fibroid disease. Three cavities apparently arose spontaneously during the period of our observation and the patients at no time had any expectoration, even under postural drainage. One of these cavities disappeared in three months, one became filled with débris; one increased in size and six months later caused a spread of the tuberculosis, which then produced sputum containing tubercle

bacilli. These 3 cases are of particular interest since no expectoration was present at any time under close observation; all the cavities were definite roentgenologically. Two cases with blocked cavities had thoracoplasty performed; in both, positive sputum appeared for the first time after the second stage when only the original cavity was present and without additional lesions. This phenomenon was probably due to the forced opening of an occluded bronchus as a result of the thoracoplastic collapse.

Cases

1: No. 5,490; male; aged 30; admitted in 1929 with a 10-cm. cavity in the left upper lobe. The cavity decreased rapidly in size, and in 1931 was represented by a 5 x 2-cm. dense apical shadow. At this time the patient had no expectoration whatever. In 1933 this dense area was replaced by a cavity with a fluid-level, but no expectoration was present. In February, 1935, a phrenic paralysis was produced and 11 days later the cavity was replaced by a dense shadow similar to that of 1931. He now has a blocked cavity, but at no time had expectoration, although his cough reflex is easily evoked. Whether there was a spontaneous absorption of débris or whether the cavity content escaped our attention, we do not know.

2: No. 6,425; female; aged 22; admitted in 1931 with bilateral cavitation. The right lung did well under pneumothorax. The left cavity measured 7 x 12 cm., and the sputum was positive. The fluid in this cavity increased until February, 1934, when the cavity contained a high fluid-level and a small air-bubble. At this time the patient raised 4 cc. of mucoid sputum which was persistently negative. In May, 1934, the cavity had been replaced by a dense shadow without an air-bubble, and the heart and trachea were displaced toward this side. In August, 1934, a small air-bubble reappeared; then disappeared again in November, 1934. All smears and cultures of sputum were negative. On March 23, 1935, the patient had a severe attack of coughing, and suddenly raised 300 cc. of thick purulent sputum, which was positive on plain smears. X-rays taken the same day showed the original 7 x 12-cm. cavity, with the heart and trachea back in normal position. The interesting feature of this blocked cavity is the appearance and disappearance of the gas bubble. The cause of the block was probably an intrabronchial plug. (Figure 6.)

3: No. 6,676; female; aged 46; admitted in December, 1931, with a 4 x 5-cm. cavity at the left apex, and with positive sputum. In March, 1933, the cavity appeared as a dense shadow and the sputum was negative. In May, 1933,

the cavity reappeared, with positive sputum. In February, 1934, the cavity was again replaced by a dense shadow and the sputum was negative. In June, 1934, the cavity reappeared, with positive sputum; in October, 1935, it was again replaced by the dense shadow, with negative sputum. The block in this case was probably an intrabronchial plug. (Figure 7.)

4: No. 7,576; male; aged 39; diagnosed as pulmonary tuberculosis in 1919, with haemorrhage and positive sputum. Since that time the patient has had an haemoptysis, varying in amount from 4 to 8 oz., every 18 months to 2 years. Admitted in October, 1933, following a haemorrhage and since that time he has had no expectoration, but X-ray showed a 6-cm. multilocular excavation of the right upper lobe. Following a phrenic paralysis the cavities decreased greatly in size; and for the past two years there has been no haemoptysis or expectoration. The fibrocavernous type of lesion suggests a block which is probably due to fibrosis in the cavernous area, possibly analogous to the extrabronchial fibrosis seen in the autopsied cases previously mentioned.

Figs. 6A, B, C & D. Case 2. Showing alternate blocking and opening of the cavity.
Figs. 7A, B, C & D. Case 3. Showing alternate blocking and opening of the cavity.

5: No. 7,805; female; aged 30; admitted in June, 1934, with cavity in the left lower lobe and positive sputum. Institution of left pneumothorax resulted in good collapse, with disappearance of all expectoration. On admission there was also a small nodular area in the 3rd interspace on the right side; this nodule disappeared, but reappeared in April, 1935. In August, 1935, it was replaced by a rarefied area 2 cm. in diameter, which steadily increased in size and soon became surrounded by exudative lesions, which resulted in positive sputum. Pneumothorax on this side resulted in accentuation of the cavity-walls, and then subsequent good closure with no expectoration. The interesting feature in this case lies in the formation of a cavity and its increase in size for two weeks with no expectoration.

6: No. 7,893; female; aged 32; had rheumatic heart disease since childhood. Tuberculosis was diagnosed in 1934, when the patient was pregnant and had positive sputum. X-ray showed a bilateral fibroid apical lesion with a 4-cm. cavity at the apex of the left lower lobe. On being put to bed all expectoration ceased, and the cavity became much smaller. It became larger 6 months later; then smaller 3 months afterwards and then again larger; and at the present time is 4 cm. in diameter. The patient was delivered of a normal child, showed no clinical activity, and has had no expectoration for 15 months. The cause of the cavity-block may be a fibrocaseous constriction because of the character of her lesions.

FIG. 6A

FIG. 6B

FIG. 6C

FIG. 6D

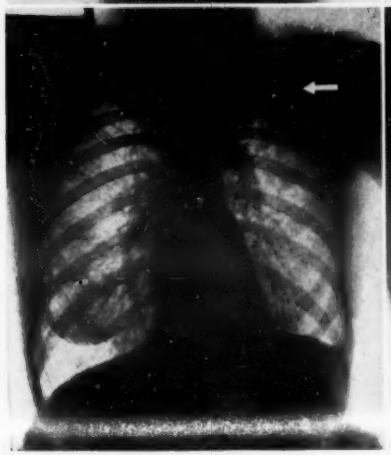

FIG. 7A

FIG. 7B

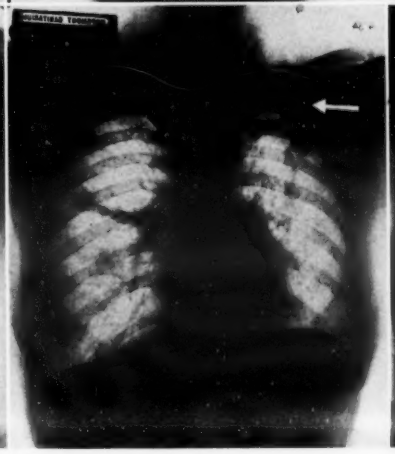

FIG. 7C

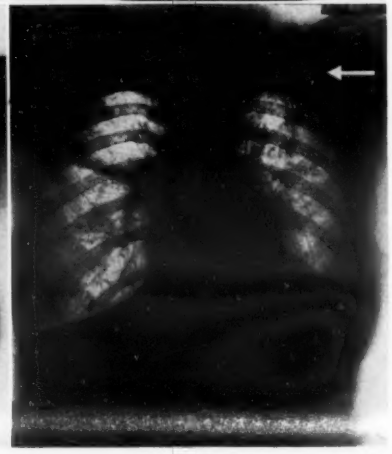

FIG. 7D

643

7: No. 7,929; female; aged 18; admitted in August, 1934, with positive sputum and two 5-cm. cavities with fluid-levels in the upper lobe of the left lung. Pneumothorax could not be induced. However, all expectoration ceased in September, and in January, 1935, the lower cavity had disappeared. The upper cavity continued to show an increasing fluid level; and in April, 1935, all air had been absorbed and the cavity had been replaced by a dense oval shadow. The interesting features in this case include the absorption of air while the cavity was blocked, the increase of fluid, and the persistence of the cavity while the surrounding pulmonary tissue appeared normal. The block in this case may be due to a bronchial plug.

8: No. 8,033; female; aged 27; admitted in April, 1933, with positive sputum and a 4-cm. cavity at the apex of the right lower lobe. The cavity enlarged to 4 x 6 cm., and developed a thick wall and a fluid-level, but the sputum became negative. A lipiodol injection was then done; the bronchi about the cavity were well visualized, but the dye did not enter the cavity. Pneumothorax was instituted in August, 1933, and the cavity decreased in size, but positive sputum was not obtained until two years later.

9: No. 8,226; female; aged 26; admitted with positive sputum and exudative disease, with a 4-cm. cavity with fluid-level at the right base, which contained also a small localized pneumothorax. Intrapleural pressure was -5, -2, but intracavity pressure was -8, $+5$. Gentian-violet was injected into the cavity, but has not appeared in the sputum, although the cavity decreased to 2 cm. in diameter in a period of four months.

10: No. 8,190; male; aged 33; admitted with positive sputum and a multilocular cavity at the left apex. One week later all expectoration ceased, but X-rays showed no change. One month later the patient coughed up some thick pus, which was positive, but expectoration lasted only one day. Pneumothorax was then instituted and accentuated the walls of the cavity, but expectoration is still absent.

11: No. 6,335; female; aged 35; admitted in June, 1931, with positive sputum and a 4-cm. cavity at the right apex. In July, 1932, all sputa became negative on guinea-pig inoculation and cultures, but X-rays continued to show the cavity. The patient had repeated attacks of pleuritis over the right apex (pleural rub and X-ray shadows were both present). In 1935 a pneumothorax was begun, resulting in selective collapse of the upper lobe and accentuation of the cavity. All sputa have been negative to the present time, a period of 3 years. The fact that the sputa became negative after pleuritis and that the patient's lesion is predominantly fibroid may point to an extrabronchial fibrosis as the cause of the block.

12: No. 7,995; female; aged 25; admitted in November, 1934, with exudative lesions at the right apex and a 4-cm. cavity with fluid-level at the right base. Prior to admission the sputum had been positive, but after admission no sputum could be obtained. The cavity decreased in size; but the exudative area enlarged and pneumothorax was begun despite lack of expectoration. The pneumothorax accentuated the walls of the cavity, which finally disappeared. In February, 1935, a small nodule appeared in the left subapical area, and in May, 1935, a small but definite cavity appeared at this site. This cavity disappeared 5 months later. During all this time various attempts were made to obtain sputum, but unsuccessfully. The problems presented by this phenomenon are the cause of the formation of this cavity, the origin of the air in the cavity, and the cause of its disappearance.

13: No. 7,586; female; aged 20; admitted in November, 1933, with positive sputum and a 6-cm. multilocular cavity with fluid-level at the base of the left upper lobe. Pneumothorax was unsatisfactory and was discontinued, and phrenic paralysis failed to affect the cavity. In April, 1934, the patient had severe pleuritis (evidenced also by X-ray), following which cough and expectoration ceased. After the pleuritis the upper lobe showed retraction, and the cavity then measured 4 cm. Expectoration occurred only for 2 weeks in January, 1935, and during one day in June 1935, both occasions resulting in positive sputum. The block is probably a bronchial plug.

14: No. 7,278; male; aged 46; admitted with positive sputum and a 6-cm. cavity in the 2nd interspace. Pneumothorax failed. Following a phrenic paralysis in April, 1934, the cavity measured 5 cm. and had moved up to the 1st interspace, but all sputa were repeatedly negative. Thoracoplasty was performed by Dr. R. B. Bailey, and following the second stage the patient coughed up several plugs of tenacious pus and the sputum became positive. At this time the cavity was much smaller and no additional disease was present. The block in this case was a bronchial plug, which was present for 15 months and which was dislodged by thoracoplastic collapse.

15: No. 6,751; female; aged 27; admitted in February, 1932, with positive sputum and a 5-cm. multilocular cavity at the apex of the left lung. Pneumothorax could not be induced owing to adhesions, and phrenic paralysis failed to close the cavity. In April, 1934, all sputa became negative, but because definite cavitation was present a thoracoplasty was performed by Dr. John Alexander. After the second stage the sputum became positive and the operation continued to obliterate the cavity. This case also shows a 15-months-old bronchial block dislodged by thoracoplasty.

SUMMARY

The anatomical studies reveal that pulmonary cavities may exist without communicating with the tracheobronchial tree, that they may be small or large, that they may be present with or without a fluid-level, that they may enlarge while blocked, that they may be productive of cavity signs, and that they present the same gross and microscopic pathological characteristics as do those cavities which communicate with the bronchial tree. The block may be intracavitary, intrabronchial or extrabronchial. The intracavitary block is caused by a filling-up of the cavity with caseous débris; the intrabronchial block may be due to purulent plugs or an inflammatory bronchial occlusion; and the extrabronchial block is fibrogenic. We realize that other causes of block may exist, but they were not present in our series.

The clinical studies tend to confirm the anatomical findings. The blocked cavities varied from 4 to 12 cm. in diameter. Fluid was present in 7 of the 15 patients with blocked cavities (cases 1, 2, 3, 7, 8, 9, 12). The blocked cavity in case 5 enlarged, that in case 6 varied in size, and those in cases 9 and 12 decreased in size, whereas 10 cavities showed no change in size. The ability of the cavity-wall to absorb air while blocked is shown in cases 1, 2, 7, 12, while in case 2 air disappeared and reappeared. Spontaneous cavity-formation occurred in cases 1, 5 and 12. During the existence of the block, positive physical signs of cavity were present in 4 patients (cases 2, 4, 11, 15), suggestive in 2 patients (cases 1, 7), and absent in the others.

The cause of the block cannot be given accurately, but was probably due to extrabronchial constriction in 2 patients (cases 4, 11) and intrabronchial plugging in 10 patients (cases 1, 2, 3, 7, 8, 9, 10, 13, 14, 15). Contributory factors in the production of the block was a phrenic paralysis in case 14, and pleuritis in cases 11 and 13. The intracavitary pressure in one blocked cavity with fluid approximated atmospheric.

DISCUSSION

This study refutes the beliefs, (1) that blocking a draining bronchus causes healing of a cavity; (2) that an intrabronchial lipiodol injection which fails to enter a cavity means that no cavity is present; and (3) that blocking the draining bronchus of a cavity means the disappearance of the physical signs of cavity.

The healing of pulmonary cavities is not a simple anatomical process,

but one that includes many unknown physiological aspects. Some deductions with regard to the closure of cavities may partly explain the problem. If the air in a blocked cavity is absorbed, resulting in closure of the cavity, one must assume that, among other factors, the cavity-wall was soft enough to be capable of collapsing and the surrounding lung was able to expand to fill up the space formerly occupied by the cavity. If, however, the cavity-wall is too rigid to collapse or the surrounding lung too extensively infiltrated or bound by pleural adhesions, then such a cavity will persist and contain fluid or air, or both, at approximately atmospheric pressure. Evidence has been produced by several of our clinical cases to show that air or fluid may pass in either direction through a cavity-wall. Blocked cavities may remain stationary in size, enlarge, decrease or vary in size, according to the controlling factors present and according to the activity of the tuberculous lesions.

The presence of physical signs over blocked cavities proves that cavity signs are not entirely dependent upon a patent bronchus. Certainly the amount of movement of the overlying bony cage, the depth of the cavity in the lung and the condition of the surrounding tissue are important controlling factors.

The prognosis of blocked cavities does not appear to differ from that of open ones, for, even in the small number of cases presented in this study, blocked cavities have been found in the cadaver, have been found to reopen with accompanying positive sputum, have been found to produce a spread of the tuberculous disease and, in a few cases, to be compatible with good general health and show no signs of clinical activity. The variable behavior of blocked cavities produces a number of problems as to the mode of therapy. A certain number of these cavities probably become filled with caseous débris, and by inspissation and encapsulation become clinically inactive. But, if blocked cavities show both air and fluid, or alternately open and close, or extrude positive sputum at irregular intervals, or produce pleuritis or spread of the disease, then collapse therapy should be given a trial. In our hands pneumothorax has been of greater value than phrenic paralysis. Three cavities closed by thoracoplastic collapse showed no unusual phenomena. It is possible that collapse may only displace a blocked cavity rather than produce approximation of its walls, but in our cases such an event did not occur, probably as a result of the active control by the cavity-wall of the intracavitary pressure and content, resulting in absorption of the entrapped air or fluid. The fact that the same patho-

logical characteristics are present in the walls of open and closed cavities lends support to the active treatment of cavities with closed bronchi.

CONCLUSIONS

1. Cavities which do not communicate with the tracheobronchial tree may exist in the lung (in 14 per cent of our series).

2. Blocked cavities throw new light upon the physiological problems dealing with the production, behavior and healing of cavities.

3. Blocked cavities require the same treatment as those which communicate with the tracheobronchial tree.

The authors wish to express their appreciation for the assistance and review given them by Doctors John Alexander, Kennon Dunham, Carleton B. Peirce and George L. Leslie.

POSTMORTEM BRONCHOGRAPHY[1]

DAVID SALKIN, A. V. CADDEN AND R. B. McINDOE

Postmortem roentgenography of the chest has been a well-known procedure for many years, but postmortem bronchography has been done only sporadically. Even then it was usually performed after removal of the lungs from the thoracic cage. Despite this fact, medical literature contains many allusions and theoretical deductions based upon the supposed appearance of the dead bronchoalveolar tree. Our own studies on this subject were begun October 24, 1933, as an aid to routine autopsy. We have found, however, that not only did it help actual dissection and give valuable information when autopsy could not be done, but that it also cast new light upon some of the anatomical and physiological conceptions concerning the lung and its pathological processes.

The material in this study included a total of 79 deaths, of which 70 were associated with pulmonary tuberculosis, 3 with heart disease, and one each with bronchiectasis, silicosis, abscess, empyema, carcinoma, and normal chest. Autopsy was done in 42 cases (53 per cent).

The technique has been detailed in a previous paper (1), but a short résumé will be given here. After the death of the patient, the body is placed upright in a chair designed by Mr. H. E. Holtzman (figure 1). This chair is mounted on wheels and its seat slopes backward to keep the body erect; the back of the chair contains a 14 x 17-inch casette. The radiopaque medium is injected slowly through the glottis, trachea, or into a cavity directly through the chest-wall. This is done under direct fluoroscopic vision. The fluidity of the mixture is observed by noting the change of fluid-levels in the bronchi when pressure is made upon the chest. We have used the following radiopaque media with good results: barium, potassium iodide, sodium bromide, hippuran, brominol and lipiodol. Our routine solution consists of a mixture of potassium iodide 10 gm., barium sulphate 20 gm., and milk 100 cc. This medium produces a striking radiographic picture and the barium leaves a white trail in bronchi, alveoli and cavities, which is easily traced

[1] From the Hopemont Sanitarium, Hopemont, West Virginia, and the Michigan State Sanatorium, Howell, Michigan.

during dissection. This mixture is sufficiently fine to show up immediately the feathery clusters presented by filled alveoli.

The findings have been grouped under the headings of the visualization of alveoli, bronchi, cavities, massive haemorrhage, bronchopleural fistula, pneumothorax and pneumoperitoneum.

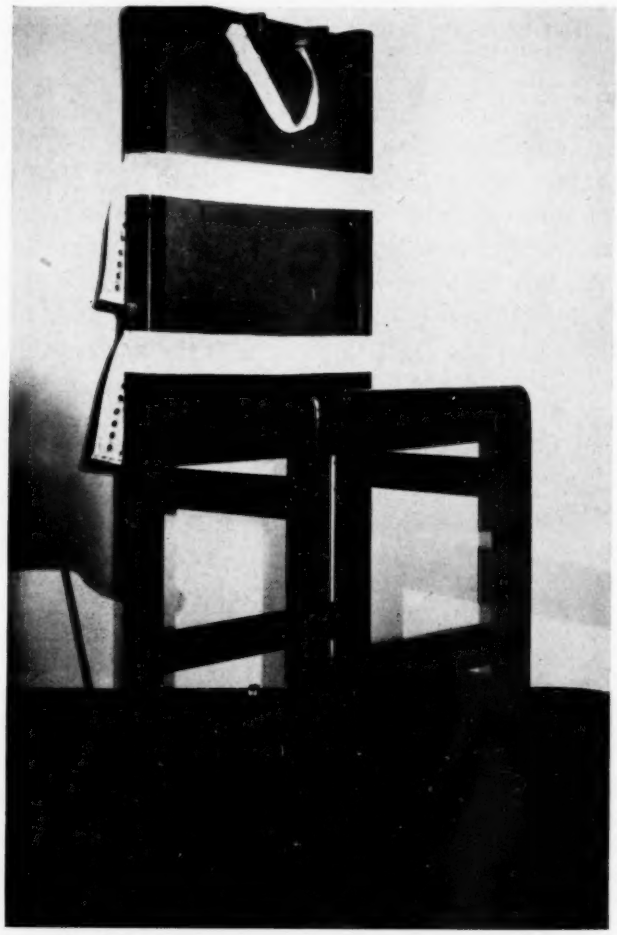

Fig. 1. Photograph of chair used in postmortem bronchography.

VISUALIZATION OF ALVEOLI

When the thorax of a cadaver is opened the lungs do not collapse completely but retain a small amount of air, known as "minimal air." It is believed that this retention is due to the collapse of the small

bronchi and the entrapping of the air in the alveoli. As a result of this theory, injection of the dead tracheobronchial tree with a radiopaque medium should show no filling of the alveoli because they cannot be reached. We have found, however, that the minimal air can be entirely replaced by many liquids. The resulting X-ray picture shows an abundance of alveolar filling resembling a "tree in full bloom." The rapidity with which the alveoli are visualized depends solely upon the viscosity of the solution used. The absence of alveolar filling occurs only when definite morbid changes are present, and depends entirely upon anatomical rather than physiological disturbances.

Depending upon the number of air-sacs filled with the radiopaque dye, the resulting X-ray film may show isolated, scattered or dense groups of alveoli. We have found repeatedly that, no matter how dense the alveolar filling may appear roentgenologically, actual dissection reveals that more than half of the lobules have not filled. The reason, we believe, is due to the entrapping of the air by the dye. Greater alveolar filling may be obtained by the use of a less viscous solution, by slower injection, and by manual pressure upon the chest to force the air out. By this method we have been able to effect an almost complete alveolar filling in many cases, as seen at autopsy.

Good alveolar filling was always seen in lungs, which showed no disease involving the air-sacs or bronchi. But we have also seen good filling in the presence of (a) emphysema and (b) scattered areas of pneumonic infiltration. In our series, the 10 cases of emphysema showed the best alveolar filling, and required more solution to fill the bronchoalveolar tree than did the normal lungs (figure 2). In these emphysematous lungs the alveolar filling was in all cases nearly complete, as confirmed by autopsy. The presence of scattered infiltration varied the degree of alveolar filling, depending upon the number of normal alveoli still present. That this number may be considerable, is shown by the good filling obtained in 2 cases of miliary tuberculosis, 13 cases of nodular infiltration and one case of dense exudative disease (figures 3, 16).

The absence of alveolar filling occurred in (1) absence of alveoli, (2) collapse of alveoli, (3) previous filling of alveoli, (4) bronchial obstruction, (5) bronchiectasis, and (6) entrapped air. No alveolar visualization occurred when the air-sacs had been destroyed and replaced by caseation, cavitation and fibrosis. Alveolar filling was absent also when the alveoli had been collapsed and their walls approximated

Fig. 2

Fig. 3

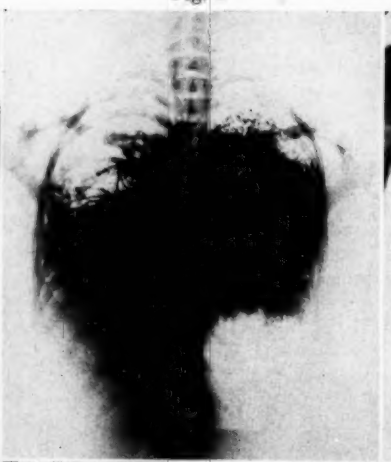

Fig. 4

Fig. 5

Fig. 6

Fig. 7

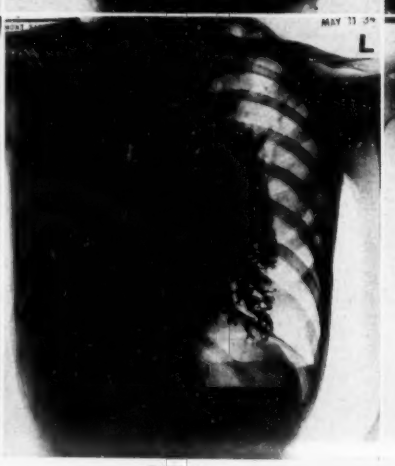

Fig. 8

Fig. 9

by pneumothorax, pleural effusion, tumors, atelectasis, and pressure from a displaced mediastinum (figures 4, 5, 8, 9). The alveoli did not admit the radiopaque medium if they were already filled with pneumonic exudate, blood, oedema, or involved in an infarct (figures 5, 6, 7). If the bronchi were blocked, dependent alveolar filling did not occur. Bronchiectasis also produced an absence of alveolar filling, due probably to intrinsic obstructive suppuration; this feature will be discussed later (figures 3, 5, 8). In 10 cases alveolar filling was absent despite the normal appearance of the bronchi and alveoli, and was probably due to entrapped air by the solution injected.

Fig. 2. Alveolar filling in emphysema. No attempt made to fill upper halves.

Fig. 3. Left side shows good alveolar filling in face of exudative infiltration. Right side shows basal bronchiectasis; no attempt made to fill upper half.

Fig. 4. Absence of alveolar filling under pneumothorax. Bronchopleural fistula with perforation at arrow. The dye ran along the lung to the dependent portion and then fell into the pleural space: note rain-drop effect prior to falling.

Fig. 5. Absence of alveolar filling associated with pneumothorax, consolidation and bronchiectasis.

Fig. 6. Case with miliary tuberculosis. Absence of alveolar filling on left side due to haemorrhagic exudate in alveoli. Right lung shows good alveolar filling: no attempt to fill upper half.

Fig. 7. Death from myocardial failure. Oedema at pulmonary bases. Note increase of alveolar filling at apices distant to oedema. Infarct on left side shows no filling.

Fig. 8. Absence of alveolar filling associated with bronchiectasis, pneumothorax, and consolidation.

Fig. 9. Right side shows kink of major bronchus, and pneumothorax. Left side shows good alveolar filling with lipiodol, and pneumoperitoneum.

In a tuberculous lung, which may contain bronchial pus-plugs, bronchiectasis, cavities, emphysema, and some normal tissue, all varieties of alveolar filling may be expected, depending upon the type and degree of pathological process present. In such a lung partial alveolar filling was commonly seen, especially in the presence of incomplete pneumothorax, scattered infiltration, or obstruction of some of the bronchi.

VISUALIZATION OF BRONCHI

The roentgenological appearance of the tracheobronchial tree was the same postmortem as antemortem. The course, size and position of the bronchi were unchanged and any deviation from the normal was due to a definite anatomical disturbance. Kinks and blocks were the chief abnormalities noted in this study.

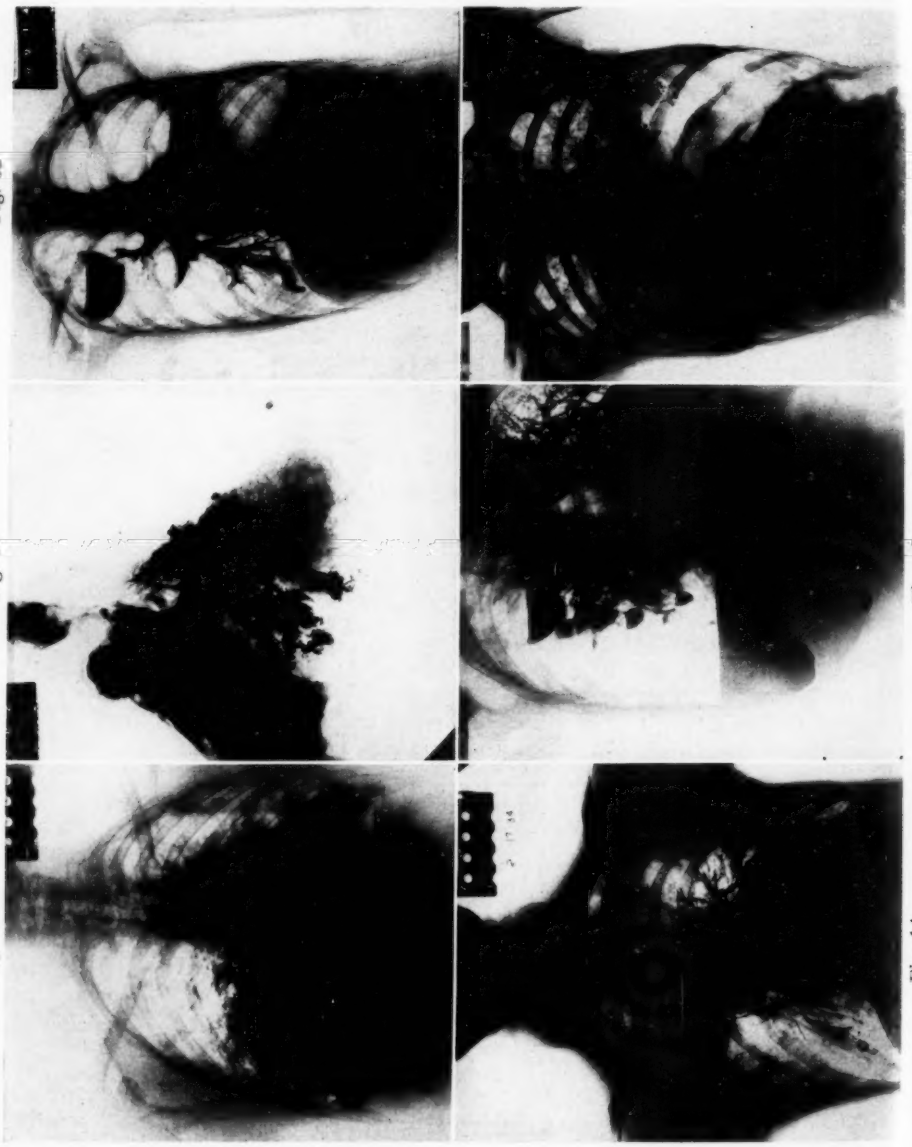

Fig. 10 Fig. 11 Fig. 12 Fig. 14 Fig. 15 Fig. 16

Kinking of a major bronchus occurred in two cases and was due to dense adhesions (figure 9). Kinking of the smaller bronchi was not observed except when associated with bronchiectasis or fibrosis.

Blocking of a major bronchus occurred in 12 cases, of which 4 came to autopsy (figure 10). In three of the cases the block was due to dense fibrosis involving the bronchus, and in one case was due to a pus-plug. In the 8 cases which were not autopsied, 2 were associated with massive haemoptysis, the obstruction probably due to a blood-clot; 3 cases were obstructed probably by extensive fibrosis; in 3 cases the cause could not be determined. Not one case showed dependent atelectasis. One block of particular interest occurred in the largest of the three divisions of the main bronchus to the left lower lobe (figure 11). The block was

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Fig. 10. Blocking of main bronchus to the left upper lobe by fibrosis. No atelectasis present.

Fig. 11. Bronchial block, 48 hours' duration and due to pus-plug. No atelectasis. Lungs were injected prior to removal from chest: haemostat inserted in interlobar fissure.

Fig. 12. Block of cavity at right apex due to tuberculous bronchitis. The cavity did not fill by tracheal route and was injected through the chest-wall. Left side showed a spontaneous haemopneumothorax.

Fig. 14. Death caused by massive pulmonary haemorrhage. Note the central type of bronchial block especially about the offending cavity.

Fig. 15. Bronchopleural fistula distant from the excavated areas of the lung.

Fig. 16. Miliary tuberculosis and pneumoperitoneum. This plate was taken 30 minutes after injection of lipiodol. Note the good alveolar filling at both bases and absence of bronchial visualization.

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due to a pus plug and was estimated to have occurred 48 hours before death. The dependent lung was voluminous and showed no signs of atelectasis.

Blocking of the smaller bronchi may be general or local. Generalized blocking of the minor bronchi occurred in 2 cases, one of which was associated with extensive tuberculous bronchitis and the other with myocardial failure. Localized blocking of the minor bronchi occurred, in some degree, in most cases and was due to intrabronchial secretion, pus, blood, or entrapped air (figure 6).

Bronchiectasis was frequently seen at the apex in areas of chronic disease and near cavities, but it was also seen in 14 cases (20 per cent) at the base in areas relatively free from parenchymal disease (figures 3, 5, 8). This high incidence was probably due to the presence of the factors underlying bronchiectasis, namely, infection, bronchial secretions,

partial obstruction, and cough. As previously stated, the alveoli dependent upon these dilated bronchi did not fill with the dye.

VISUALIZATION OF CAVITIES

We have observed two types of cavities, those that communicated freely with the tracheobronchial tree and those that were blocked. In this series, only cavities over 3 cm. in diameter were studied, since the smaller ones presented many technical details, which made the results unreliable. A total of 147 cavities was examined, and 21 of these (14 per cent) did not communicate with bronchi (figure 12). In a previous paper (1) the blocked cavities were described in detail, but a brief summary will be given here. The causes of block were found to be intracavitary, intrabronchial, and extrabronchial. The intracavitary block occurred in 3 cases, in which the cavities were filled so tightly with a fibrinogelatinous débris that no dye could enter from the bronchi. The extrabronchial block occurred in 2 cases, in which the bronchi were incorporated into the dense fibrosis surrounding the cavity-wall. The intrabronchial cause included obstructing plugs and tuberculous bronchitis. Bronchial plugs were found in 3 cases, and consisted of a tenacious mixture of pus, mucus, and débris firmly fixed in the lumen near its opening into the cavity. Tuberculous bronchitis occurred in 7 cases, in which the mucosal inflammation and swelling occluded the lumen with subsequent incorporation of the bronchus into the caseous wall of the cavity.

The bronchial drainage was studied in 142 open cavities. In only two cases was the drainage accomplished by several bronchi, and in the remaining 140 cavities by one bronchus. This number included 94 cavities situated in the upper lobes and above the level of the main upper bronchi, and 46 were located in the lower lobes and below the main lower bronchi. The point of origin of the draining bronchus was designated as dependent or arising from the lower, middle, or upper third of the cavity-wall. The upper-lobe cavities showed the following drainage points: Dependent 37 per cent, lower third 34 per cent, middle third 23 per cent, upper third 6 per cent. In the lower-lobe cavities the bronchi originated as follows: Lower third 35 per cent, middle third 27 per cent, upper third 38 per cent (figure 13). Thus, in an upright position, only 37 per cent of the upper cavities were drained continually clean and the remainder accumulated fluid until the level reached that of the bronchus. In the lower-lobe cavities a similar condition existed

with an additional lack of dependent drainage. Since drainage begins only when débris is extruded into the bronchus, many cavities probably retain the fluid for long periods of time.

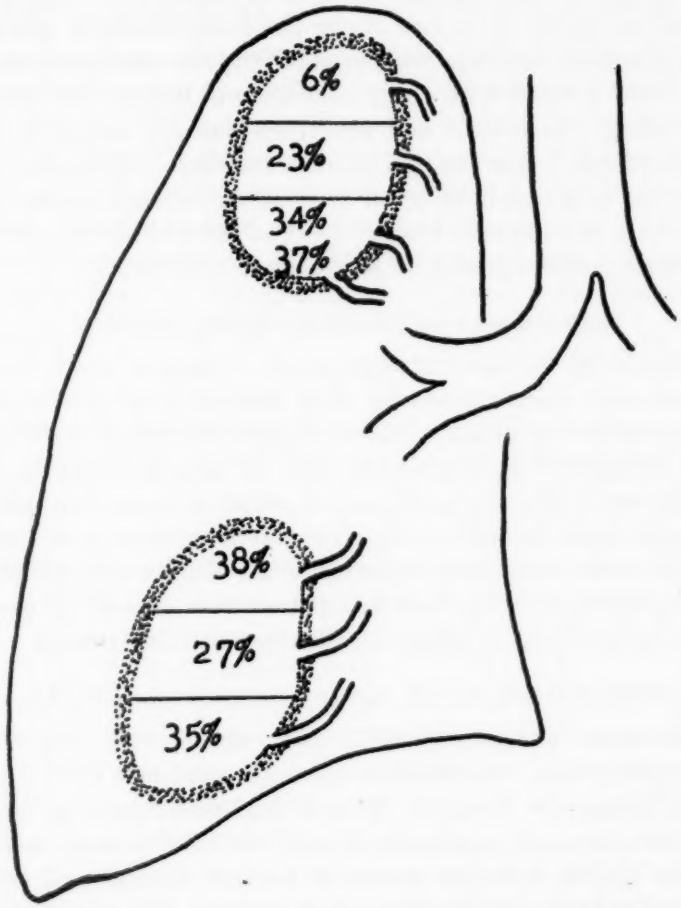

Fig. 13. Diagram showing the location and percentages of drainage points of upper and lower lobe cavities.

VISUALIZATION OF MASSIVE HAEMORRHAGE

Six cases in this series died a few seconds after a massive pulmonary haemorrhage, and three of them came to autopsy. A plain postmortem X-ray film showed blood-levels in 4 cases. Bronchography revealed no obstruction in the trachea, but the large bronchi about the offending cavity were blocked with blood-clot. Injection of the barium mixture

showed two types of block: in 3 cases the solution was stopped abruptly in the large bronchi, and in the other 3 cases the solution was stopped only in the central portion of the bronchi and continued to flow along the sides, resulting in a hollow-pipe appearance (figure 14). Such a block was produced by the retraction of the blood-clot leaving a small space between it and the bronchial wall, in which the dye was deposited. The blood showed a small spill to the contralateral lung in one case. No alveolar filling was present and atelectasis was not seen. In four of these cases a needle was inserted through the chest-wall into the cavity and into the larger bronchi; in all of these the bronchi showed clotted blood and the cavities fluid blood. In the 3 cases autopsied, the cavity blood remained uncoagulated for several hours after death.

VISUALIZATION OF BRONCHOPLEURAL FISTULAE

Bronchopleural fistulae were observed in 7 cases, of which four were associated with spontaneous and three with artificial pneumothorax. The fistulous communication was strikingly demonstrated fluoroscopically as the injected dye was seen to leave the lung and enter the pleural cavity (figures 4, 15). In the 3 cases autopsied, however, only one of the perforations could be seen in the gross. It is interesting to note that only three of the perforations occurred in the vicinity of a cavity. The remaining four were at the base and distant from a cavity or gross disease, the causative agent being a small tuberculous infiltration.

VISUALIZATION OF THE LUNGS UNDER PNEUMOTHORAX

Pneumothorax was present in 22 cases, of which 12 were artificial and 10 spontaneous. Localized collapse occurred in 6 cases and considerable collapse in 16 cases. Pleural fluid was present in 14 cases, spontaneous haemopneumothorax in one case, and no fluid in 7 cases. The lower pleural limit was curved in 7 cases, straight in 2 cases, irregular in 1 case, and not determined in 12 cases. This appearance bore no relationship to the degree of pneumothorax collapse, phrenic nerve paralysis, or pleural fluid.

The degree of alveolar filling under pneumothorax depended upon the degree of pulmonary collapse (figures 4, 5, 8, 9, 15). In 10 cases with a subtotal collapse no alveolar filling was present. In 12 cases with partial collapse, alveolar filling was good in 4, partial in 5, and absent in 3 cases. This filling depended upon the degree of collapse of the more normal portions of the lungs. The bronchi under pneumothorax were

grouped more closely, but showed no kinks or blocks with the exception of 2 cases of bronchiectasis. The cavities presented no unusual findings.

VISUALIZATION OF THE LUNG WITH PNEUMOPERITONEUM

Pneumoperitoneum was seen in 7 cases, of which three were artificially produced and four resulted from perforated intestinal ulcers. Since bronchography was done in an upright posture, the intraperitoneal air was concentrated under one or both leaves of the diaphragm, resulting in 12 subphrenic air spaces measuring from 1 to 5 cm. in height (figures 9, 16). The alveolar filling in the overlying lung was good in 8 cases and absent in 4 cases. In this latter group, pneumothorax was present in 3 cases and bronchiectasis in one case. Thus, not one case of pneumoperitoneum affected alveolar filling in the lungs.

SUMMARY

Postmortem bronchography visualized bronchi, alveoli, and pulmonary abnormalities in conformation with definite anatomical features. The alveoli showed good filling in a normal lung, in emphysema, and in the presence of scattered areas of disease. Alveolar filling was absent when the alveoli had been destroyed, collapsed, previously filled with exudate, transudate or blood, in bronchial obstruction, and in bronchiectasis. Generalized bronchial block, which produced an X-ray appearance of a "dead tree without leaves," was rare. Localized areas of bronchial block were common and were due to intrabronchial secretions, pus, blood, and the entrapping of the air by the medium used. Blocking of a major bronchus occurred in 12 cases (15 per cent), and was not associated with atelectasis. The average tuberculous lung showed all varieties of alveolar filling and bronchial blocks.

Pulmonary cavities were found to be blocked in 14 per cent and open to the tracheobronchial tree in 86 per cent. Only a small number of all cavities had dependent drainage, and most efferent bronchi arose from the upper parts of the cavity-wall. Massive haemoptysis produced a characteristic picture:—clear trachea, complete or central block of the large bronchi about the cavity, clotted blood in the bronchi, and fluid blood in the cavity.

Pneumothorax collapsed the alveoli and prevented them from filling with the radiopaque dye. The bronchi under pneumothorax showed no kinking or distortion. Bronchopleural fistula was demonstrated strik-

ingly in 7 cases, four of which were situated distant to a cavity or gross disease. Pneumoperitoneum failed to affect alveolar filling in the lungs.

DISCUSSION

The ease with which the minimal air of the lung can be replaced by various solutions casts doubt upon the belief that the air is entrapped by the collapse of the small bronchi. A more probable cause lies in the incomplete collapse of the lung resulting from damaged elastic fibres due to death, and the retention of a small amount of air. In discussing the appearance of a lung filled with lipiodol, Sante (2) has stated that at first only bronchial filling is present because the alveolar air is entrapped by the oil; several minutes later, however, the alveoli are filled because the obstructed air in the sacs has been absorbed by the circulating blood and the oil is sucked in by the negative pressure so produced. Our experience with lipiodol injection postmortem has been as follows: injection of lipiodol a few minutes to one hour after death resulted, first, in visualization of the bronchi only, followed by a gradual filling of the alveoli, which was completed within 30 minutes (figure 16). Warming the lipiodol accelerated the rate of alveolar filling. Certainly there was no circulating blood in the cadaver to produce a similar picture in the dead and living lungs. We must then suppose that the rate of alveolar filling depends clinically upon the viscosity of the medium injected, and the degree of filling upon the amount of dye not coughed up from the lung. Normal alveoli always tend to fill with the dye, and when they do not the reason lies in some anatomical disturbance.

The absence of atelectasis in the presence of 12 blocks of major bronchi and numerous blocks of smaller bronchi, many of which were long standing, lends clinical support to Van Allen's theory of interlobular air communications. It is apparent that in some cases more than a mere blocking of a bronchus is necessary to produce atelectasis. The entrapping of the air by the dye in the smaller bronchi, and the resulting lack of alveolar filling bears out the clinical experience of the failure to visualize a group of diseased bronchi at one time and its demonstration at another time. It stresses also the importance of repeated lipiodol injections in suspected cases of bronchiectasis if one examination proves negative.

We wish to stress the absence of alveolar filling dependent upon dilated bronchi. In all the postmortem cases the bronchi contained sufficient pus to produce occlusion. We have been convinced repeatedly

that the radiopaque solutions we have used can penetrate any part of the lung that air can enter; this is further confirmed by the abundance of alveolar filling observed in so many of our cases. We believe, therefore, that if the dye did not enter the alveoli, neither did inspired air before death. This feature was noted clinically in 68 cases of bronchiectasis, which had instillations of halogenated oils by cannula, catheter and bronchoscope. In all of these cases postural drainage had been instituted previously, and at the time of bronchography 5 cases had no expectoration and the remainder varied from 2 cc. to 200 cc. In 63 cases showing definite bronchiectasis, no alveolar filling was seen in 61 cases and slight filling in 2 cases. In 5 cases of suspicious bronchiectasis slight alveolar filling was present. We believe that these findings add to our knowledge of the physiology of the lung under bronchiectasis. Certainly the absence of alveolar filling indicates that little or no air reaches these alveoli, but, instead of showing atelectasis, they appear normal, or show emphysema or pneumonitis. This fact further strengthens the theory of interlobular air channels. Such an area has not only a stagnant respiratory circulation, but probably has also a stagnant vascular and lymphatic circulation. It is not surprising that such a lung should be regarded as a source of inflammation and infection, and it is possible that the pneumonitis, locally and distantly produced, may be due to it rather than to the bronchi whose secretions are often well drained. We are, at the present time, concerned with the physiology of such a lung and the prevention of bronchiectatic pneumonia by pneumothorax despite its lack of effectiveness against the diseased bronchi themselves.

The existence of blocked cavities and their clinical importance has been described in a previous paper. The determination of the point of origin of the efferent bronchus has direct clinical application. Since only a small number of all cavities have dependent drainage with the patient in an upright posture, one cannot stress too highly the importance of change of position and the need of postural drainage to place the draining bronchus in a dependent site. This procedure is especially true in lower-lobe cavities; in fact, in all cavities showing a fluid-level.

That massive haemorrhage does not cause death by suffocation, is shown by the fact that the trachea was clear in all cases and that a "spill-over" to the opposite lung occurred in one case. The fact that the blood in the cavity remains fluid, coagulating only upon its extrusion into the bronchi, adds another factor, which must be considered in the evalu-

ation of any procedure for the control of haemoptysis in pulmonary tuberculosis. Many cases of haemorrhage are probably controlled by intrabronchial clotting and an increase in the cavity pressure above that of the bleeding vessels.

Pneumothorax produces an alveolar collapse depending entirely upon its size; in a partial pneumothorax many alveoli are open and fill readily with the dye. Contrary to some opinions, kinking of the bronchi did not occur under pneumothorax unless produced by bronchiectasis. Pneumoperitoneum did not produce any alveolar collapse, and clinically we have not seen any benefit resulting from pneumoperitoneum upon a tuberculous lung. The aid given to routine autopsy by postmortem bronchography is especially shown in the demonstration of bronchopleural fistulae.

CONCLUSIONS

1. Postmortem bronchography is an aid to routine autopsy in cases dying from pulmonary tuberculosis, and may be of great value when autopsy cannot be obtained.
2. It gives additional information about the postmortem appearance of alveoli, bronchi, cavities, haemorrhage, pneumothorax, and bronchopleural fistula.
3. It brings to light new physiological problems dealing with atelectasis, haemorrhage, pneumothorax, and pneumoperitoneum.
4. The existence of blocked cavities is shown.
5. The drainage points of open cavities are determined.
6. Some observations are made on the physiology of the lung with bronchiectasis.

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THE PUNCH BIOPSY IN THE DIAGNOSIS OF TUBERCULOSIS OF THE KNEE JOINT[1]

MICHAEL BURMAN, HARRY FINKELSTEIN AND LEO MAYER

The punch-biopsy instrument which has been developed in connection with the arthroscope allows the removal of synovial specimens through the same puncture wound used for arthroscopy. Theoretically, it is possible to remove specimens under good visual control; practically, however, specimens have to be removed blindly, although the jaws of the instrument can be accurately localized within a particular region of the knee joint. This is the major defect of the instrument. Part of the difficulty might be corrected were it possible to distend the joint through an irrigating attachment to the conchitome, since much of the fluid is lost on withdrawal of the arthroscope.

A good-sized specimen can be removed, one adequate enough to make a definite diagnosis. The joint space is rarely so small that it is not possible to open the jaws of the instrument; and rarely, too, the size of the cutting part, which is larger than the calibre of the bore of the conchitome, will not allow its introduction beneath a partially adherent patella. Yet, despite these disadvantages, we have had fair success in the 28 cases in which 30 biopsy specimens were removed.

Greatest interest centres naturally in those cases in which tuberculosis of the knee is suspected. Our series is small, since many tuberculous knees are recognized clinically, roentgenologically, or by other methods of laboratory examination. It is not necessary to do a biopsy examination if the diagnosis is established by other methods.

Six positive biopsy specimens, that is, positive for tuberculosis, were obtained in 8 cases of tuberculosis of the knee joint. In one, a woman of 35, who had been treated for villous synovitis for two years, a frozen section of the biopsy specimen revealed the presence of tuberculosis and an immediate fusion was accordingly done. No guinea-pig inoculation or tuberculin test had been previously done in her case.[2]

[1] From the Hospital for Joint Diseases, New York City, the Services of Doctor Mayer and Doctor Finkelstein.

[2] We have been able in another very recent case, in which the diagnosis was uncertain, to demonstrate very definitely the tuberculous nature of the disease process by frozen section of the biopsy specimen. Immediate fusion was done. The tissue section confirmed the diagnosis by frozen section.

A child of $3\frac{1}{2}$, in whom culture of the synovial fluid had been previously sterile, showed a positive biopsy specimen in the presence of a positive tuberculin test and a subsequently positive guinea-pig inoculation from fluid obtained at the time of arthroscopy. A very interesting positive biopsy specimen occurred in a woman of 27, who had developed a cold abscess of the head of the gastrocnemius muscle. There was previous evidence of tuberculous disease of the spine and of the opposite spontaneously fused knee. It became important to know if communication existed between the knee joint and the cold abscess in the gastrocnemius head. The separate identity of the cold abscess of the gastrocnemius head was maintained. The clinical picture and the

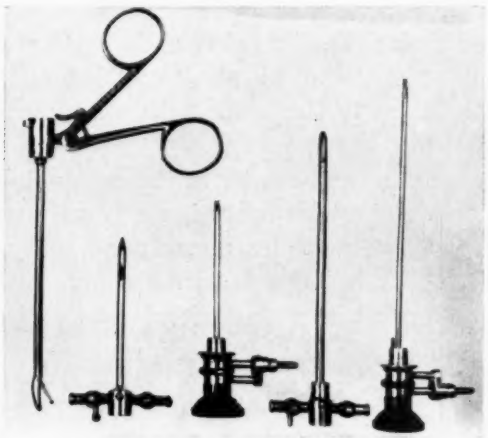

Fig. 1. The punch-biopsy instrument is at the left

roentgenogram were not clear. A guinea-pig inoculation of fluid previously removed from the knee was reported negative, although it was positive from fluid removed at the time of arthroscopy. Her tuberculin reactions to quantitative dilutions were strongly positive. In a young man of 27, who showed tuberculosis of an elbow and later tuberculosis of the lungs, the tuberculin reaction was only slightly positive and guinea-pig inoculation had been negative from fluid from the now involved right knee. The biopsy specimen was positive for tuberculosis. Fluid injected into a guinea pig from material obtained at arthroscopy was again negative for tuberculosis. A woman of 64, in whom no laboratory methods for the detection of tuberculosis had been done, demonstrated a positive biopsy specimen, which accorded with her

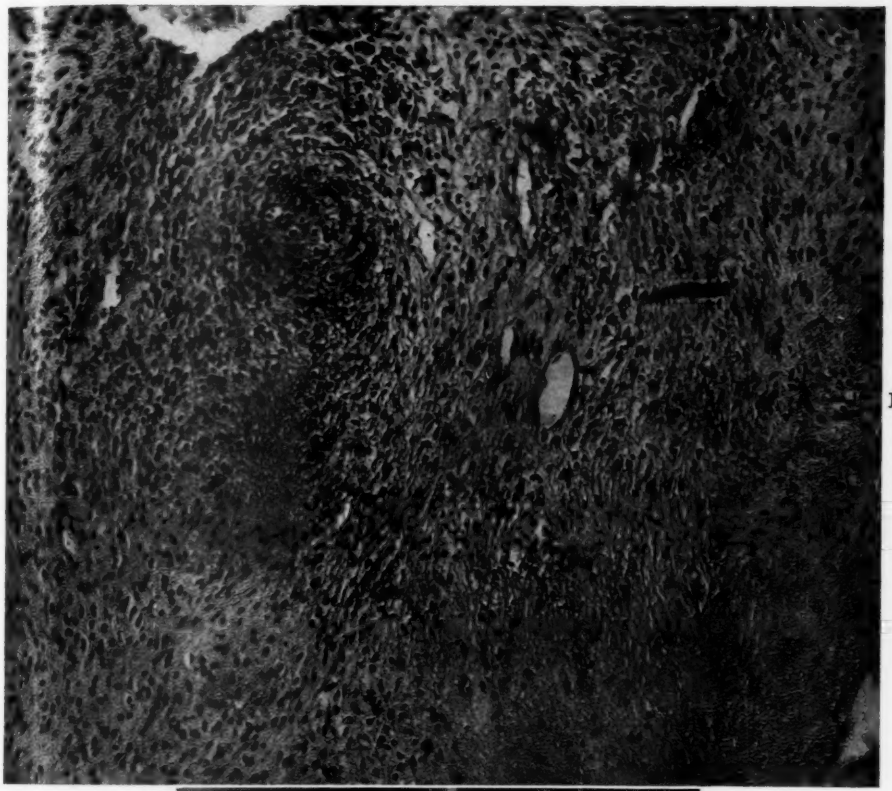

Fig. 2

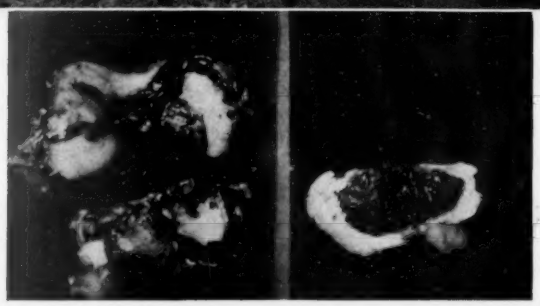

Fig. 3

Fig. 2. Section of a biopsy specimen taken from the knee joint of a child of 3½ years of age. A tubercle is present at upper left. At lower right, the beginning of an area of caseation necrosis is seen.

Fig. 3. The excised joint surfaces. Note the cold abscess in the tibia.

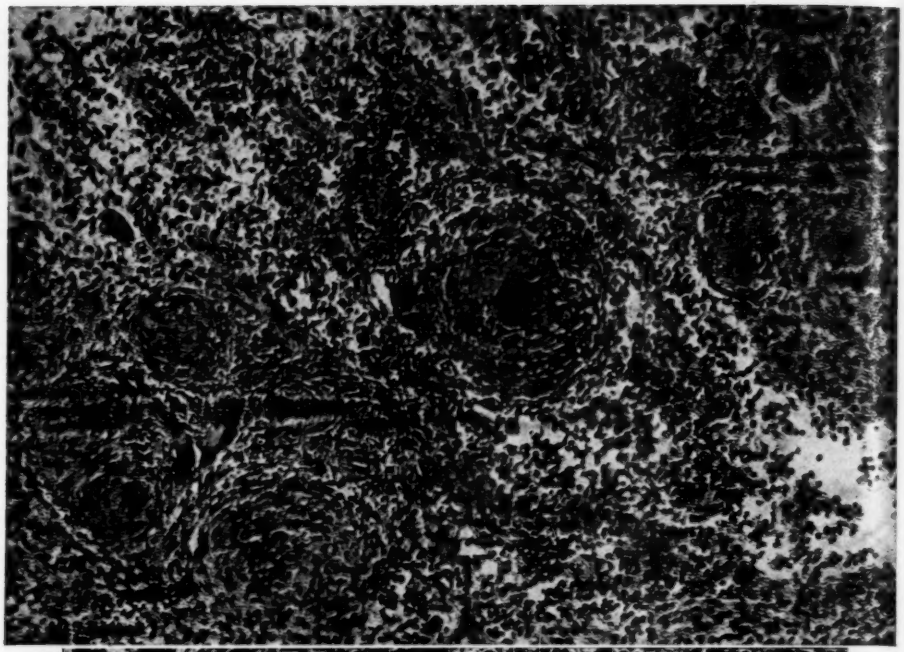

Fig. 4

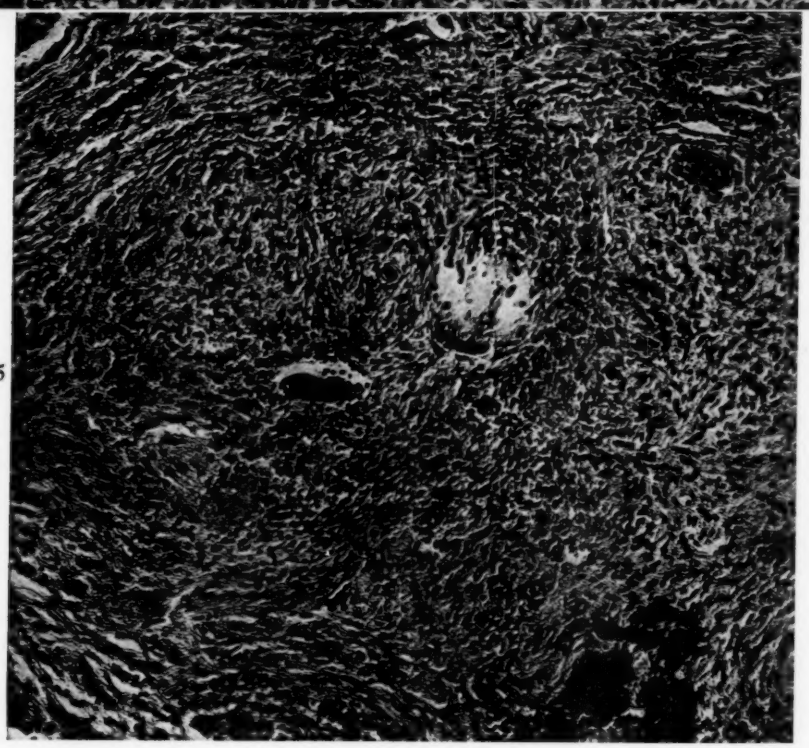

Fig. 5

clinical picture. A man of 56, in whom a diagnosis of nonspecific synovitis was entertained, revealed a positive biopsy specimen. Guinea-pig inoculation was positive also for tuberculosis from fluid obtained at the time of arthroscopy.

There were two cases with nonspecific synovial changes in the biopsy specimens, proved subsequently at operation to be derived from tuberculous joints. One occurred in a girl of 23, in whom it was not possible to secure large enough specimens because of the marked narrowing of the joint space. The guinea-pig inoculation was positive on tissue removed at the time of biopsy. A tuberculin test was not done. The other patient was a woman of 21, in whom the biopsy specimen revealed only a nonspecific, chronic synovitis. Nor did the gross appearance of the opened joint apparently warrant a diagnosis of tuberculosis, and therefore a synovectomy was done. The tissues of the knee being reported as tuberculous, a fusion was done afterward. The guinea-pig

Fig. 4. Section of a biopsy specimen removed from the knee joint of a 64-year-old woman. The diagnosis of tuberculosis is easily made.

Fig. 5. Section of tissue removed from the knee joint at the time of operative fusion several weeks later. The diagnosis of tuberculosis is again confirmed.

inoculation was negative for tuberculosis and the tuberculin reaction was only slightly positive.

A man of 47, who at the time of first examination certainly did not show evidences of tuberculosis of the knee, developed later a tuberculosis of that joint. His tuberculin reaction was negative and the biopsy specimen showed a haemorrhagic synovitis.

Of the cases in which biopsy specimens revealed a nontuberculous condition within the knee joint, nine only were checked subsequently by open operation. In these, the nontuberculous state of the joint was substantiated. Several of these cases closely simulated tuberculosis, so that clinical differentiation was not possible. Thus, a girl of 13, who had been followed for many years because of a destructive arthritis of the knee joint, and who presented repeated positive tuberculin reactions, did not nevertheless have a tuberculous knee joint, both by biopsy specimen and by the examination of the tissues excised at operation. Guinea-pig inoculation had never been done; but, at a previous operation seven years before at another hospital, tuberculosis had not been disclosed. Another young girl of 8 with a nonspecific,

chronic synovitis of the knee, in whom tuberculosis of the joint had always been suspected, revealed a negative biopsy specimen and negative tissue specimens removed at the time of operation. The tuberculin reaction had been negative on two occasions and the guinea-pig inoculation had also been reported as negative. It has been possible to rule out tuberculosis in a boy of 12, whose arthroscopic picture, biopsy speci-

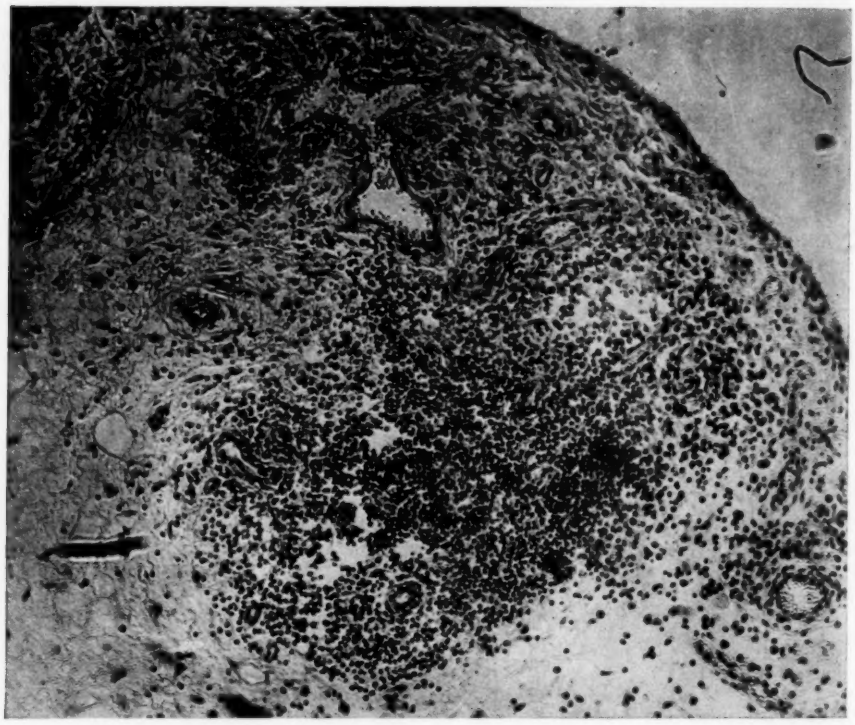

Fig. 6. Section of a biopsy specimen removed from the knee joint of a boy of 12, in whom tuberculosis was suspected. A nonspecific chronic synovitis is present.

men, tuberculin reaction and guinea-pig test all mitigated against disease specificity. The further course of the disease seems to substantiate the nontuberculous nature of his disease. In many of the other cases, the clinical picture, supported by other laboratory data, is enough to rule out tuberculosis. In only one of these did the patient present a positive tuberculin reaction. This patient, a young man of 27, subsequently had a synovectomy, and the nontuberculous nature of his affection was confirmed.

There were 5 unsatisfactory specimens in all. One of these was unsatisfactory because the specimen had dried; the others showed connective tissue or fat covered by a thin synovial lining. In none of these was there any serious reason to consider tuberculosis.

The guinea-pig test was invariably negative in the nontuberculous group; the tuberculin reaction was negative in all but two, as noted.

This consideration does not of course indicate fully the diagnostic problem presented by each case, since the clinical picture has not been presented. It is only our intention to show that the biopsy specimen is a pretty accurate measure of the specificity or nonspecificity of the disease process within the joint. It is sometimes quite difficult to prove the tuberculous nature of the disease process in the knee joint. Any method that offers a fair chance of success, both negatively and positively, should be used. Guinea-pig inoculation and the demonstration of the tubercle bacillus are the only other positive methods, besides the histopathological picture of tuberculosis. Any one of these may be wanting; yet the demonstration of one is enough to warrant a diagnosis of tuberculosis. The agreement of two or three methods renders the diagnosis irrefutable. The tuberculin test can only be considered as a sign-post, for it may be negative in frank tuberculosis of the knee, or it may be positive in a nontuberculous knee. Objection may be raised that the guinea-pig inoculation and cultural methods are time-consuming, a period of many weeks elapsing before a final report is given. In a disease as chronic as tuberculosis, so short a period of time should mean nothing, and these tests should always be done. Yet, the removal of the biopsy specimen is so simple and the nature of the disease revealed so quickly, even by frozen section, that it is bound to have a great practical appeal. There should be no antagonism between any of these methods, and one should support the other.

One method of obtaining material from a joint suspected of being tuberculous for culture and guinea-pig inoculation involves a very simple way, which most probably is used widely, though we have seen no reported description of it. It has been used at the Hospital for Joint Diseases for some time and we credit Doctor Walter Galland for its introduction. It consists in using the saline washings of the joint, after the fluid has been instilled into the joint for some minutes. In a child, in whom the removal of a biopsy specimen was objected to, the saline washings injected into a guinea pig confirmed a suspected diagnosis of

tuberculosis. We can offer no exact figures of failure or success; but, if it succeeds once, it can succeed again, especially in joints without fluid.

It is not our purpose to review the literature on the various diagnostic tests for tuberculosis. We can only refer the reader to several recent papers by Blair and Galland, Blair and Hallman, Milgram, Sundt, and especially to a paper by Siemens. Siemens secured biopsy specimens through a tiny arthrotomy opening. He notes its simplicity and that it was accurate in 100 per cent of his cases. In no case, he emphasizes, in which a negative specimen was secured, was tuberculosis later demonstrated. In any case, either the punch-biopsy method, as described here, or the method of Siemens is much simpler than the more radical methods of biopsy removal advocated by Hibbs and his co-workers.

Nor can the objection be raised that the trauma of examination by arthroscopy followed by the removal of biopsy specimens is damaging to the knee. It is not. This is warranted now by the instances in which the method has been used. In two acutely inflamed joints, these procedures were done without perceptible alteration in the state of the joint or alteration of the temperature curve for the worse.

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TUBERCULOUS TRACHEOBRONCHITIS[1]

The Rôle of Bronchoscopy

PAUL C. SAMSON[2]

It is now generally agreed (Clerf (1), Tucker (2), and Myerson (3)) that except in rare instances the presence of active pulmonary tuberculosis is not a contraindication to bronchoscopy. The widening recognition of tuberculous tracheobronchitis[3] as a definite clinical entity demands that a bronchoscopic examination be frequently used for a final diagnosis. Within the limits of bronchoscopic vision this can be done with a high degree of certainty when the lesions seen are considered in conjunction with the history and physical examination. In selected cases bronchoscopic aspiration and chemical shrinkage of congested and oedematous mucosa will give relief from distressing respiratory symptoms; occasionally such treatment may be a life-saving measure.

BRONCHOSCOPIC DIAGNOSIS

It has been emphasized that tuberculous tracheobronchitis should be differentiated bronchoscopically from nonspecific ulcers, erosion from lymph nodes, syphilis, neoplasm and rhinoscleroma. The descriptions given in the following five paragraphs are based in part upon a personal communication from Dr. Albert C. Furstenberg (4).

The tuberculous process is characterized by a chronic thickening and congestion of the mucosa. Jackson (5) describes a peculiar type of pale cyanotic tint as typical. Petechial haemorrhages may be present. In active advanced cases mucosal ulceration occurs, which in our experience is more often diffuse or confluent than circumscribed. The typical tuberculous tracheal lesions are found in the lower third of the trachea on the posterior or posterolateral wall; they are usually associated with a unilateral or bilateral bronchial involvement. When the trachea and one stem bronchus are affected the tracheal-wall involvement is usually

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[2] Anna Bissell Memorial Fellow in Thoracic Surgery.

[3] In this communication, "tracheobronchitis" is used as a comprehensive term, including specific mucosal or submucosal infection of the trachea or bronchi, or of both.

more advanced on the same side as the diseased bronchus. Both circumscribed and diffuse tuberculous lesions, however, have been described in all portions of the trachea. Tuberculous lesions found in the upper fourth of the trachea only, may be rarely considered secondary to an advanced laryngeal tuberculosis. In the stem bronchi circumscribed lesions appear to have a predilection for the posterior walls and mouths of the secondary bronchi, but frequently the lesions are sufficiently diffuse to involve the bronchi circumferentially. At times nonspecific inflammatory changes and even ulcerations are seen in the trachea or bronchi. Since these often regress as the tuberculosis becomes inactive and the cough subsides, it is important that they be distinguished from a true tuberculous involvement. Because it is difficult to differentiate a typical lesion of either type by their gross appearance, Furstenberg believes that a biopsy is often necessary to differentiate a specific from a nonspecific lesion.

Bronchial lymph nodes occasionally rupture into the lower air-passages. The symptoms are then generally typical of foreign-body obstruction and are characterized by violent paroxysms of coughing, livid cyanosis and a feeling of suffocation. Bronchoscopic inspection may reveal a perforating ulcer, usually affecting the mesial wall of one of the stem bronchi near the tracheal bifurcation. The expectoration of disintegrated bronchial lymph-node elements, often mixed with blood, the presence of a perforation in the characteristic location and radiographic evidence of hypertrophied bronchial lymph nodes will suffice to confirm the diagnosis.

Syphilis of the lower air-passages may occasionally be encountered and is usually a tertiary manifestation of the disease. The gumma in various stages of development may be found in any part of the tracheobronchial tree. Tertiary tracheobronchial syphilis may produce varying degrees of obstruction, although it is noteworthy that this lesion seldom produces cyanosis or any of the signs of severe respiratory embarrassment. Through the bronchoscope one observes a constructive process with ulceration, but with very little tendency to bleed when traumatized. Biopsy is usually necessary to determine the true identity of this lesion. Evidence of tertiary syphilis in other parts of the body, blood-serological examinations and therapeutic tests will aid in establishing a diagnosis.

Bronchogenic carcinomata are usually encountered after the age of forty. Their presence may be suspected because of persistent cough, haemoptysis, dyspnoea on exertion, pain in the chest, and loss of weight. In the late stages secondary pulmonary suppuration is almost inevitable

because of bronchial occlusion. The lesion, as viewed through the bronchoscope, may be either a fungating partially or completely obstructing mass, which bleeds easily when traumatized, or an ulcer with rolled indurated edges. Surrounding submucosal infiltration may suggest an extension of the process. In cases of suspected malignancy, biopsy necessarily must be employed to establish a diagnosis.

Rhinoscleroma usually appears in the form of nodules in the mucous membrane of the nose and nasopharynx after the fourth decade of life. The nodules coalesce, to form an irregular infiltrative mass of a chronic inflammatory character. The process may be slowly progressive with the eventual involvement of the tracheobronchial tree. Here it is widely disseminated. The lesion is hard, and the surface is a dark brownish-red shade, and shows little or no tendency to ulcerate. Marked regression and fibrosis occur following irradiation, but the lesions tend to recur. The final diagnosis of the disease is usually determined by special pathological studies of tissue removed at biopsy.

BRONCHOSCOPIC TREATMENT OF TUBERCULOUS TRACHEOBRONCHITIS

In the group of patients with tuberculous tracheobronchitis who have distressing respiratory symptoms, the bronchoscopist is able to give treatment of definite value although at times it is only palliative. In a patient recently seen who was having considerable difficulty in raising large amounts of thick tenacious sputum, bronchoscopic examination revealed a nonulcerative lesion in the left stem-bronchus. The calibre of the bronchus was reduced because of distinct mucosal oedema. The mucosa was carefully shrunken with equal parts of 10 per cent cocaine and 1-to-1000 adrenalin solution and the size of the lumen was thereby greatly increased. Following this treatment the patient has continued to raise her sputum easily.

In many patients the rapid development of symptoms of respiratory obstruction demands immediate relief which can be afforded by aspiration of thick secretions or mucous plugs. The aspiration can be repeated as often as necessary. The treatment of crusting ulcers appears to be particularly difficult. In case 2, to be described, the crusts caused repeated obstruction, and the development of alarming respiratory symptoms necessitated their frequent removal. With each instrumentation the ulcers bled and the resulting crusts became larger. All cases of this type are probably hopeless.

In selected cases circumscribed stenoses will be benefited by dilatation,

if this is done carefully. This treatment should be used only when there is no evidence of surrounding active tuberculous mucosal inflammation. If this condition is present, experience has shown that attempted dilation of a stenosis or forced passage of a bronchoscope will result in ulceration.

The dangers of too frequent bronchoscopies must not be forgotten. Acute oedema of the larynx may necessitate a tracheotomy, and this should never be withheld if the indications are clear. In our cases tracheotomy has served three purposes: (1) to afford breathing space because of an oedematous larynx; (2) to facilitate repeated low bronchoscopic and catheter aspirations through the tracheotomy incision; and (3) to allow the passage of a long intubation tube beyond a low tracheal stenosis.

CASE SUMMARIES

Since 1929 bronchoscopic examinations have been performed at the University of Michigan Hospital on 24 patients with active pulmonary tuberculosis in whom a specific involvement of the trachea or bronchi was suspected. Two patients without definite roentgenographical evidence or physical signs of pulmonary tuberculosis were examined bronchoscopically, one because of sputum which was persistently positive for acid-fast bacilli and the other because of an haemoptysis of unexplained origin. In both, a tuberculous bronchitis was discovered. Among the 26 patients thus examined a diagnosis of tuberculous tracheobronchitis was made in seventeen. In the eighteenth patient a definite tracheal ulcer was seen by laryngoscopic mirror examination. The results of the examinations in the 18 patients form the basis for this study.

Elsewhere, Barnwell, Littig and Culp (6) have described in detail the signs and symptoms of tuberculous tracheobronchitis and have included 7 representative clinical histories. Bugher, Littig and Culp (7) have presented the results of microscopic examinations of the trachea and bronchi in a series of 122 cases of active pulmonary tuberculosis. This number represents all patients dying of pulmonary tuberculosis upon whom necropsies were performed during the last eight years at the University Hospital.

A combination of several of the following signs and symptoms in each case has been considered of sufficient importance to require a bronchoscopic investigation: constant wheezing, either inspiratory or expiratory or both persisting after all sputum has been raised; extremely thick,

tenacious sputum difficult to raise; marked variation in the amount of sputum from day to day; abnormally large amounts of sputum; frequently or persistently positive sputum in spite of apparent control of the parenchymal pulmonary lesion; unexplained elevations of temperature; and intermittent areas of atelectasis as seen in serial roentgenograms of the chest. Persistent parasternal rhonchi are important symptoms in stenotic lesions (McConkey and Greenberg (8)). Varying degrees of dyspnoea on exertion may be present even though the vital capacity is insufficiently low ordinarily to be accompanied by dyspnoea (cases 7, 9 and 10). The persistence of several of these signs and symptoms can be made the basis for a prebronchoscopic diagnosis of tuberculous tracheobronchitis if the examiner keeps the possibility of this complication in mind (Barnwell and Littig). In the present series a definite presumptive diagnosis was made in 12 patients and confirmed by bronchoscopy in eleven. In the other patients bronchoscopy was done to establish the presence or absence of tuberculous tracheobronchitis in the face of somewhat indefinite symptoms before proceeding with any major form of pulmonary-collapse therapy.

The patients are divided into two groups. In the first group, numbering 12 cases, the patients were considered to have late manifestations consisting of ulcerative or stenotic lesions, or both. In the second group, numbering six cases, bronchoscopy showed non-ulcerative and non-stenotic lesions. The patients presented submucosal tubercles, diffuse thickening and reddening or granularity of the mucosa. Morphologically, these lesions have been considered as early manifestations of tuberculous tracheobronchitis. In several of the patients repetition of the bronchoscopy has given valuable information as to the progressive or regressive changes in the tracheal and bronchial lesions. A summary of each case, containing the indications for bronchoscopy and the positive bronchoscopic findings, follows.

Ulcerative and Stenotic Tracheobronchitis

Case 1 (174, 048): T. S., a white female, 43 years of age. On July 1, 1927, complained of wheezing, which she referred to the left chest. Later a roentgenological diagnosis of moderately advanced left pulmonary tuberculosis with cavity was made, and the patient was sent to the Michigan State Sanatorium. In spite of a left temporary phrenic paralysis and pneumothorax with an eventual 90 per cent collapse, there was no decrease in the patient's sputum, which remained persistently positive. In the fall of 1930 the patient began to

have increasingly severe attacks of dyspnoea with respiratory difficulty in both inspiration and expiration. The sputum was exceptionally thick and tenacious. There was a loud tracheal rattle. The pulmonary tuberculosis continued to progress unfavorably. A presumptive diagnosis of stenotic tuberculous tracheobronchitis was made.

Bronchoscopy: December 30, 1932 (J. C. Jones (9)): The mucosa of the upper trachea was slightly injected and thick gelatinous sputum was present. In the lower trachea there was a stenosis which barely admitted a large aspirating tip. A no. 12 oesophageal bougie was passed through the stenosis with difficulty. The stenosis was circular, fibrotic, nonulcerating and did not bleed readily. The area beyond the stenosis could not be inspected. The secretion was highly positive for acid-fast bacilli. The bronchoscopist's diagnosis was tracheal stenosis and tuberculous tracheitis.

The patient had an undue amount of respiratory distress during bronchoscopy, and several hours later a tracheotomy was necessary, followed by bronchoscopic aspiration of the secretion through the tracheotomy incision. The following day, because of an increase in dyspnoea and cyanosis, further bronchoscopic aspiration through the tracheotomy incision was done by J. H. Maxwell (10). The previous trauma from bronchoscopy had caused ulceration of the apparent annular constriction which had been smooth and firm at the time of the first examination. During the following four days three more bronchoscopic aspirations were necessary because of severe dyspnoea and cyanosis. Each time, crusts and secretions were found blocking the stenosed tracheal lumen. On one occasion a 10-cm. oesophageal intubation tube introduced beyond the constriction gave complete relief for forty-eight hours.

Bronchoscopy: January 4, 1933 (A. C. Furstenberg (10)): The bronchoscope was passed through the tracheotomy incision. The previously observed stenosis was ulcerated and had the appearance of granulation tissue. The bronchoscope was passed through the stenosis, and extensive lesions were seen in the left stem-bronchus, sufficient almost totally to occlude it. The ulcerative lesion extended into the right stem-bronchus for a considerable distance. This granuloma was covered with secretion which seemed viscid. Crusts had been formed which were largely responsible for the obstruction to breathing.

The patient died on the same day. At necropsy there was diffuse ulceration of the entire trachea extending into the first portion of the right stem-bronchus. The left stem-bronchus was partially stenosed 6 mm. below the carina. The mucosa beyond the stenosis was granular and irregularly ulcerated. Microscopic examination showed ulcerative tuberculous tracheobronchitis. The tracheobronchial lymph nodes contained active miliary tubercules microscopically, without gross evidence of tuberculous involvement.

Discussion: In retrospect, the possibility of tracheobronchial involvement from the beginning of this patient's illness should be considered. Necropsy

showed no evidence of direct extension from the tracheobronchial lymph nodes to the tracheobronchial mucosa. This case illustrates well the rapidity with which ulceration can take place. A comparison of bronchoscopic examinations showed that the stenosis had become granular and slightly ulcerated within twenty-four hours, and that diffuse ulceration had occurred in the trachea within four days. Of added importance is the evidence of progression of the tracheobronchial disease in spite of excellent control of the pulmonary disease.

Case 2 (309, 768): L. H., a white woman of 27. This patient had moderately advanced right-sided pulmonary tuberculosis. Roentgenograms showed a right-upper- and middle-lobe atelectasis which varied from month to month. After six months' hospitalization there was an exacerbation of the wheezing and dyspnoea which the patient had first noted one year previous to the diagnosis of her tuberculosis. The sputum became positive for acid-fast bacilli in July, 1933, after a three months' period during which it had been negative. As right-sided palpable rhonchi were present, a clinical diagnosis of tuberculous tracheobronchitis was made.

Bronchoscopy: October 4, 1933 (J. C. Jones (9)): A stenosis of the trachea was found to extend from 2.5 cm. below the glottis to the carina. There was much scarring, and the mucosa was thickened and bled freely. Numerous small crusting ulcerative lesions were seen. The carina was widened. The right stem-bronchus was too narrow to admit a 7–40 bronchoscope without trauma. The left stem-bronchus was slightly narrowed and the mucosa was thickened, showing numerous small scars and ulcerating lesions. The mucosa everywhere bled freely. The picture was typical of far-advanced tuberculous tracheobronchitis, with ulceration and stenosis. The aspirated exudate showed caseous necrosis microscopically.

The subcutaneous administration of tuberculin in repeated small doses gave no systemic reaction, and there was no observable improvement in the symptoms which were referable to the patient's tracheobronchitis.

The patient was discharged to a sanatorium, and at the present time is reported to be showing slight symptomatic improvement.

Discussion: In this case, also, there was evidently a progression of the tracheobronchial involvement in spite of strict bed-rest, which was sufficient at least temporarily to control the pulmonary lesion.

Case 3 (205, 324): D. W., a white woman of 20. This patient had far-advanced bilateral pulmonary tuberculosis with cavitation; a technically satisfactory bilateral pneumothorax had been induced at the Michigan State Sanatorium.

Following a severe paroxysm of coughing without expectoration she suddenly developed marked inspiratory and expiratory distress with cyanosis. Indirect laryngoscopy showed a mass of fibrin below the cords; this was removed by

direct laryngoscopy, with resulting complete relief of symptoms. During the next four months the patient developed wheezing with expiratory difficulty; the sputum became very thick and tenacious. A clinical diagnosis of tuberculous tracheobronchitis was made.

First bronchoscopy: October 12, 1932 (Norton Canfield (10)): The laryngeal mucosa was slightly thickened and the anterior tracheal wall showed several oval areas of ulceration from the 8th to the 10th rings. The ulcers bled easily. A piece of mucosa was removed for biopsy. There was slight narrowing by scarring of the lower trachea and upper stem-bronchi. The pathological report on the removed tissue was active, chronic, caseous tuberculosis.

There was marked symptomatic relief for several weeks following the bronchoscopy. Exacerbation of symptoms, however, recurred following a severe coughing attack. Examination showed restriction of the respiratory excursions and diminished or absent breath sounds in the right chest.

Second bronchoscopy: November 13, 1932 (Norton Canfield): The trachea contained thick pus which was aspirated. The mucosa was considerably improved as compared with the previous examination. There was a patchy hyperaemia, but no ulceration as previously seen. In the right stem-bronchus, about 3 cm. below the carina, there was an ulcerated obstructive lesion with loose pieces of slough attached to its edges. Several sloughs were removed, thereby enlarging the breathing space in the right stem-bronchus. The patient was symptomatically relieved. The report on this tissue was active, chronic, caseating tuberculosis.

Following this bronchoscopy breath-sounds were heard well on the right. The right pneumothorax was abandoned without change in the patient's condition.

Third bronchoscopy: January 9, 1933 (Norton Canfield): The tracheal mucosa was intact throughout. The surface was roughened in areas, but there was no ulceration. Considerable improvement was noted as compared with the previous examination. At the carina the mucosa was hyperaemic without ulceration. The right stem-bronchus showed hyperaemia and purulent discharge, but no crusting ulcerations were seen.

The patient was free from symptoms for several months and then again developed increasing respiratory difficulty, thick tenacious sputum which was difficult to raise, and increasing cyanosis on slight exertion.

Fourth bronchoscopy: August 5, 1933 (J. C. Jones (9)): The thick tenacious sputum in the trachea was aspirated. The mucosa of the entire trachea was sclerotic and narrowed, although at this time there was no evidence of ulceration. Both stem-bronchi and all the orifices of the lobar bronchi appeared somewhat stenosed because of fibrotic infiltration and scarring. This condition was more extensive on the right side. Thick tenacious secretions were aspirated from the trachea and both stem bronchi.

August 16, 1933, it was decided that no further attempt be made to control the pulmonary lesion because of the presence of a far-advanced bilateral tuberculous tracheobronchitis and positive sputum. It was felt that effective treatment could not be offered for the pulmonary lesion, particularly since the tuberculous tracheobronchitis had developed during a period of satisfactory collapse when the patient was without sputum.

This patient's course was gradually downhill, although there was slight symptomatic improvement following the last bronchoscopy. There was roentgenographical evidence of an extension of the tuberculous pulmonary parenchymal lesion. Death occurred with typical evidence of tracheobronchial obstruction, there being increasing dyspnoea and cyanosis.

Discussion: This patient developed definite signs and symptoms of active tuberculous tracheobronchitis while her pulmonary lesions were well controlled. Therapeutically, the bronchoscopies gave temporary symptomatic relief. Diagnostically, the four bronchoscopies were of very great value because the repeated examinations clearly demonstrated the pathogenesis of stenotic lesions in this case. The ulcerations healed with a resulting hyperaemic and oedematous mucosa. Later extensive stenosis was seen as well as localized areas of scarring. This type of healing certainly could not be considered beneficial to the patient, since the tracheobronchial obstruction was undoubtedly an important factor in her death. As far as can be determined definite evidence of the healing of ulcerative lesions has not been presented elsewhere in the literature.

Case 4 (205,796): M. P., a white female, aged 29: Serial roentgenograms showed intermittent atelectasis in the right upper lobe. There were severe paroxysmal attacks of cough associated with dyspnoea; rhonchi were palpable over both lungs, and a clinical diagnosis of tuberculous tracheobronchitis was made.

First bronchoscopy: June 19, 1930 (A. C. Furstenberg (10)): The trachea was normal. On the anterior wall of the right stem-bronchus, from 4 to 5 cm. below the carina, there was an oval area of ulceration 3 cm. long. The ulcer was extensive and was covered with a membrane of the diptheritic exudate type. There were masses of granulation tissue extending into the lumen of the bronchus.

The pathological report on the biopsy specimen was: "Complete caseation necrosis. No tubercles, but the process might well be tuberculosis."

During the six weeks following bronchoscopy the patient was slightly worse objectively, there being some increase in pulse and expectoration. There were occasional periods of fever. There were increased asthmatoid attacks with dyspnoea. A definite parenchymal spread of the tuberculosis was seen in the

left lung in the roentgenograms of August 5, 1930. Another bronchoscopy was advised before pneumothorax should be tried.

Second bronchoscopy: February 5, 1931 (H. P. Nelson (9)): The lumen of the trachea was decreased and almost occluded with pus. Breathing became easier following aspiration of this material. The mucosa of the trachea was thickened and soggy and its usual lustre was absent. The tracheal rings were not visible. In the right stem-bronchus the mucosa was in a similar state, the lumen being considerably reduced. The mouth of the upper-lobe bronchus could scarcely be seen, but no foreign body or tumor was found in the mouth of this bronchus or in the main stem. No ulceration was seen. The left main-stem-bronchus also contained pus which was removed by aspiration. The mucosa was seen to have the same unhealthy appearance as on the other side.

Following the bronchoscopy an emergency tracheotomy was necessary because of obstructed breathing. The course was gradually downhill, with roentgenographical evidence of basal consolidation and gradual parenchymal spread of the tuberculosis. There was a daily septic temperature. Frequent aspirations of the tracheotomy tube were necessary. Death occurred on April 4, 1931.

At necropsy the mucosa of the bronchi was swollen, but no ulcer was seen. At the bifurcation of the trachea the bronchial lymph nodes were greatly enlarged, necrotic and caseated, and apparently constricted the orifice of the right upper-lobe bronchus. Microscopically, there were acute purulent bronchitis, chronic tracheitis, and oedema and catarrh of the larynx. No microscopic evidence of tuberculosis was found in the tracheobronchial tree.

Discussion: In this patient there was a definite spread of the parenchymal lesions following bronchoscopy and biopsy. The patient was apparently made worse by the second bronchoscopy. At the time of the first bronchoscopy a definite ulcer was seen and described below the right upper-lobe orifice. At the time of the second bronchoscopy the operator stated that no ulcer was seen. No ulcer was described at autopsy, and therefore we may assume that this lesion healed. The microscopic examination of the biopsy specimen gives further evidence of the specific nature of the originally described ulcer. This case is one of two in the series in which there was narrowing of a stem-bronchus due to enlarged peribronchial lymph nodes (compare case 15). Eloesser (11) has found that this condition occurs frequently in children: Myerson found it only rarely in adults.

Case 5 (321,896): E. B., a white female of 33: The patient had a far-advanced bilateral exudative pulmonary tuberculosis, predominantly right-sided. In September, 1933, the patient had a two-stage right-sided multiple intercostal neurectomy; this was followed by improvement in her general condition.

Serial roentgenograms showed recurrent shadows in the lungs which were

interpreted as due to obstruction of the small bronchi. There were sudden elevations in temperature without definite reason, and there was a variation in the amount of sputum from day to day. The sputum was intermittently positive and there were occasional attacks of wheezing. A clinical diagnosis of tuberculous tracheobronchitis was made.

First bronchoscopy: May 2, 1934 (Cameron Haight (9)): The trachea appeared normal except for an area immediately adjacent to the right stem-bronchus. This was an ulcerative lesion extending from the right stem-bronchus on to the right lateral wall of the trachea for a distance of about 1 cm. The right stem-bronchus was greatly stenosed by a proliferative type of fibrous tissue, which was ulcerated but which bled very little. The lumen admitted an aspiration tip without difficulty. The nonulcerated, inflammatory mass extended almost to the carina. There was no involvement of the left stem-bronchus.

After nine months' bed-rest at the Michigan State Sanatorium the patient appeared somewhat better and the wheezing was less frequent. The sputum remained intermittently positive. A second bronchoscopy to determine the extent of the tracheobronchial involvement was performed.

Second bronchoscopy: January 10, 1935 (Cameron Haight): The tracheal mucosa showed marked, diffuse inflammation. The previously described lesion on the right lateral wall of the trachea was now seen to extend for nearly 3 cm. above the carina. It appeared as a pale, yellowish-gray granuloma elevated about 2 mm. above the tracheal wall. The lesion completely involved the orifice of the main stem-bronchus, which was almost completely occluded by the process. It also involved the carina, and extended from 2 to 3 mm. along the mesial wall of the left stem-bronchus. The carina was badly diseased, and had lost its normal characteristics: no carinal spur was visible. In view of the progression of the lesion and the definite involvement of the left stem-bronchus, thoracoplasty was believed to be contraindicated. Following bronchoscopy, a superficial ulceration, slight granular excrescences and some interarytenoid swelling were seen by indirect laryngoscopy on the superior surface of both vocal cords. This ulceration disappeared within two months.

Discussion: Following her intercostal neurectomy, the patient was considered suitable for thoracoplasty. However, because of her respiratory symptoms she was bronchoscoped. Thoracoplasty was then found to be contraindicated because of evidence of progression of her ulcerative tracheobronchial lesion. Recently, there has been a slow progression of the pulmonary disease and some increase in excavation. This patient's prognosis is considered poor.

Case 6 (323,608): L. G., a white female of 33. The patient had moderately advanced left-sided pulmonary tuberculosis with cavity. Following closed

intrapleural pneumonolysis, excellent collapse by pneumothorax was obtained. Positive sputum and occasional elevations of temperature continued. The pre-pneumothorax roentgenograms showed a shadow on the right, interpreted as partial atelectasis. The patient developed a rattling sensation in her chest, and rhonchi became audible and palpable. There was considerable variation in the amount of sputum. A clinical diagnosis of tuberculous tracheobronchitis was made.

First bronchoscopy: January 12, 1935 (A. C. Furstenberg (10)): In the left stem-bronchus there was an ulceration of the mucous membrane, together with granulation tissue and exudate. These lesions began at about 2.5 cm. below the tracheal bifurcation. The process on the left virtually amounted to a series of tuberculomata. The clinical characteristics of the lesion in the left bronchial tree were typically those of tuberculosis. The granulation tissue was biopsied, but on microscopical examination turned out to be only chronic inflammation.

The wheezing improved markedly and the cyanosis practically disappeared following bronchoscopy. The patient was then given weekly roentgen-ray treatments for eight weeks, ending March 8, 1935. From April to September, 1935, there was slow symptomatic improvement. The sputum decreased from 40–60 to 10–20 gm., and was mucopurulent and watery. It was occasionally positive on direct smear. Temperature elevations were less frequent, and appetite was definitely improved.

Second bronchoscopy: June 1, 1935 (A. C. Furstenberg): The lower air-passages appeared to be definitely improved and the right stem-bronchus again showed no lesion. The diffuse ulceration in the left stem-bronchus was entirely healed, with the exception of one area about the size of a split-pea, which still showed superficial ulceration and a scant amount of granulation tissue. There was scarring in the mucous membrane of the anterior wall of the left stem-bronchus, and the lumen was very slightly narrowed, but no actual stenosis was present.

The patient's larynx was examined on numerous occasions; infiltration, mucosal granularity and actual ulceration were described from time to time. On November 14, 1934 the larynx was negative for evidence of intrinsic tuberculosis. On February 20, 1935, one month after the first bronchoscopy, it was believed that the larynx was definitely more infiltrated. Granulations were seen on the mesial aspect of the arytenoids. Two months later this condition had improved and no evidence of ulceration was seen. On June 5, 1935, following the second bronchoscopy, there was still granular thickening of the posterior commissure and only questionable evidence of ulcerative thickening of the lateral angles of the posterior commissure.

Discussion: In this patient the definite symptom-complex of tuberculous tracheobronchitis developed during a period of excellent control of the pul-

monary disease by subtotal pneumothorax. Comparison of the results of the two bronchoscopic examinations showed definite improvement which should, perhaps, be attributed to the roentgen-ray therapy. The healing in this case was manifested by considerable scar-tissue which may eventually result in stenosis of the left stem bronchus, although this is not present now. Bronchoscopy apparently caused no appreciable increase in the laryngeal disease.

Case 7 (333,036): H. O., an American Indian male of 36. The patient had far-advanced bilateral pulmonary tuberculosis with cavitation. Various collapse measures, including phrenic paralysis and bilateral paraffin pneumonolyses, had been employed to control the tuberculosis. Postoperative roentgenograms showed suggestive, but not definite, cavitation on both sides, and bronchoscopy was recommended for the purpose of obtaining differential smears from the stem-bronchi.

The sputum was persistently positive, and there were occasional temperature elevations to 99°. In spite of a vital capacity of 1,900 cc., the patient was definitely dyspnoeic when moving about in bed.

Bronchoscopy: March 13, 1935 (J. W. Strieder (9)): The tracheal mucosa showed slight injection. The carina was somewhat broadened. There was an area of granulation tissue just anterior to the anterior portion of the carina and somewhat to the right of it, extending down into the right stem-bronchus. This area was circular, and about 0.5 cm. in diameter. The mucosa of the right stem-bronchus was markedly injected and bled very easily. Below the middle-lobe orifice there were extensive areas of granulation tissue and there seemed to be a partial stenosis of the right lower-lobe bronchus, its lumen being approximately one-half normal size. Because the patient seemed to have an evident hyperplastic type of bronchial tuberculosis, differential specimens of sputum were not taken.

Discussion: The usual signs and symptoms were absent in this patient's case, and no diagnosis of tuberculous tracheobronchitis was made previous to bronchoscopy. The persistently positive sputum and the absence of definitely demonstrable cavitation, the occasional temperature elevations and the dyspnoea in spite of a vital capacity of 1,900 cc. should, however, be considered as strongly suggestive of tuberculous tracheobronchitis. The patient's condition is at present stationary. The eventual prognosis is considered poor.

Case 8 (330,720): C. B., a white male of 26. The patient had bilateral far-advanced pulmonary tuberculosis with cavitation of the left lung. The sputum was mucoid, exceptionally viscid and consistently positive. There were a marked wheeze, brassy cough and great difficulty in raising sputum. Previous laryngeal ulcerations had been present, but had healed. A clinical diagnosis of tuberculous tracheobronchitis was made at the Michigan State Sanatorium.

First bronchoscopy: February 24, 1934 (J. C. Jones (9)): The entire tracheobronchial mucosa was thickened and sclerosed, and the lumen of the trachea was narrowed. There were areas of actual ulceration and of grayish-white infiltration; healed tubercles were visible. The mucosa bled easily. The lumen of the left stem-bronchus was stenosed to a no.-16 French bougie diameter, and the mucosa in both stem-bronchi appeared similar to that in the trachea. The right stem-bronchus was narrowed to two-thirds of its normal diameter, but was less diseased than the trachea and left stem-bronchus. The bronchoscope could not be passed into either stem-bronchus. The diagnosis of ulcerating and stenosing tuberculous tracheobronchitis was made. A small piece of exudate which was coughed into the bronchoscope was found microscopically to contain a small caseating tubercle.

The patient returned to the Michigan State Sanatorium and was on strict bed- and complete voice-rest for the following year and a half. The wheezing became less prominent, and he was able to raise sputum with greater ease. His general condition remained relatively good, and there was no spread of his parenchymal pulmonary tuberculosis.

Second bronchoscopy: September 28, 1935 (Paul C. Samson (9)): The mucosa of the trachea and right stem-bronchus was slightly thickened and oedematous, but there was no appreciable narrowing of the trachea and no ulceration. The mucosa did not bleed. The right stem-bronchus was, perhaps, slightly narrowed, but a 6-40 bronchoscope could be passed with ease. The lumen of the left stem-bronchus was too narrow to allow the passage of the 6-40 bronchoscope. At the stenosis the mucosa was slightly ulcerated, and beyond there were other ulcerations, the extent of which could not be determined.

Discussion: This patient is the only one in this series with such a widespread tracheobronchial involvement whose lesions have shown any tendency to retrogress. Formerly considered to have a hopeless prognosis, he is now being reconsidered for a left-sided thoracoplasty. Since mucosal ulcers are still present in the left stem-bronchus, however, roentgen-ray therapy is being given in an attempt to heal these lesions before proceeding with the contemplated thoracoplasty. While we still consider that the prognosis of this patient is very grave because of his tracheobronchial lesions, their spontaneous regression without the formation of diffuse stenotic changes has greatly lessened the absolute pessimism with which we had previously regarded widespread tuberculous ulcerative disease of the tracheobronchial mucosa.[4]

Case 9 (307, 611): L. H., a white female of 35 years. This patient had moderately advanced left pulmonary tuberculosis with cavity. There was no marked

[4] Following roentgen therapy all visible ulcerations healed, the stenosis of the left stem-bronchus persisting. This patient recently has successfully undergone a left-sided thoracoplasty and at the present time his sputum is negative for tubercle bacilli.

improvement after sixteen months' bed-rest and the performance of a left temporary phrenic-nerve interruption. The patient developed inspiratory and expiratory wheezing, with diffuse sonorous rhonchi, most intense over the trachea. The sputum was excessive in amount, mucoid and frequently positive. There was a subjective sense of lower substernal constriction and difficulty in "getting air in." A moderate dyspnoea was noted even though the vital capacity was 1700 cc. A clinical diagnosis of stenotic tuberculous tracheobronchitis was made at the Michigan State Sanatorium.

First bronchoscopy: February 2, 1933 (J. C. Jones (9)): The trachea was slightly narrowed, and there were multiple small white areas which appeared to be old scars. There was no ulceration or bleeding. The right stem-bronchus appeared slightly narrowed, but without appreciable stenosis. The mucosa was roughened without ulceration. The opening into the left stem-bronchus, however, appeared as a slit, about 4 mm. long in the anteroposterior direction and about 1 mm. in the transverse direction. The stenosed bronchus opened and closed with respirations. No ulceration was seen. A no.-14 oesophageal bougie was passed without difficulty and appeared to stretch the stenosis. A specimen of bronchial secretion from this side was found to be loaded with acid-fast bacilli. The bronchoscopic diagnosis was tuberculous tracheobronchitis with stenosis of the left stem-bronchus. Clinically the only change following bronchoscopy was temporary increase in the amount of sputum.

Second bronchoscopy: February 15, 1933 (J. C. Jones): The left stem-bronchus did not appear to be as stenosed as previously. There was a globule of yellow, thick, purulent sputum at the orifice which was aspirated. Nos. 14 and 16 bougies were passed without difficulty and without bleeding.

Following the second bronchoscopy there was some clinical improvement, less dyspnoea and less wheezing. The sputum still remained frequently positive. There was a slight spread of the tuberculosis in the left lower lobe. In July, 1933, a subtotal lobar atelectasis was shown on the roentgenogram, but there were no clinical symptoms of the condition.

Third bronchoscopy: December 14, 1933 (J. C. Jones): The left stem-bronchus was stenosed to about 3 mm. as at the first examination. Nos. 12 and 14 bougies were passed without difficulty. There was a small amount of oozing.

The patient returned to the Michigan State Sanatorium, and over a period of six months the symptoms referable to the stenosis gradually improved. The improvement occurred *before* left pneumothorax was induced. This procedure was instituted in July, 1934, because of left-sided cavitation and positive sputum. At present the patient has no sense of substernal constriction and she wheezes rarely. Her sputum is negative. The following bronchoscopy was done immediately prior to her discharge.

Fourth bronchoscopy: July 27, 1935 (Paul C. Samson (9)). The previously described tracheal scars were not prominent. Only two were definitely seen on the right anterolateral wall about 3 cm. above the carina. The lumen of the right stem-bronchus appeared normal. The mucosa above the right upper-lobe orifice was roughened but there was no evidence of active inflammation. The stenosis of the left stem-bronchus was a vertical, slightly stellate slit, as previously described. It measured about 4 by 1.5 mm. The walls were soft and pliable, and there were definite expansion and contraction on inspiration and expiration. The mucosa was normally smooth and did not bleed. There was practically no sputum.

Discussion: This patient evidently had symptoms resulting from partial obstruction. There had been no clinical or bronchoscopic evidence of ulcerative disease. Since the stenosis was still present at the time of the last bronchoscopy, the symptomatic improvement which occurred was probably the result of a change in the character of the stenosis. The lack of an inflammatory mucosal reaction and the softness and pliability of the walls of the stenosis make it seem logical that there has been a regression of the scar-tissue formation similar to that described by Lederer in the larynx.

Case 10 (343, 129): R. N., a white male of 35 years, had a moderately advanced left upper pulmonary tuberculosis with cavitation. There was some shortness of breath in spite of a vital capacity of 2,400 cc. There was a clearly audible inspiratory and expiratory wheeze which did not entirely clear on coughing. A clinical diagnosis of tuberculous tracheobronchitis was made. The laryngeal examination was negative.

Bronchoscopy: August 30, 1934 (John Alexander (9)): The left stem-bronchus had a definitely thickened mucosa and was in places somewhat reddened, but no ulceration could be seen. The lumen of the left lower stem-bronchus was somewhat narrowed. The bronchoscope could not be passed into the left lung without force because there appeared to be a spasm of the glottis. The diagnosis was moderate stenosis of the left stem-bronchus from a tuberculous bronchitis.

With bed-rest and a left temporary phrenic paralysis the patient's condition improved. His sputum has been consistently negative since bronchoscopy, and parasternal rhonchi are still present but are much less marked than before. He has been recently discharged as apparently arrested from the Grand View Hospital, Iron Wood, Michigan.

Discussion: This patient presented an anatomical indication for thoracoplasty which, however, was not performed because of the bronchoscopic findings. His shortness of breath should be considered as important; since this was one of his original chief complaints, the possibility of tracheobronchial involvement early in his history might be postulated.

Case 11 (189,738): M. S., a white female of 29, who had bilateral, moderately advanced pulmonary tuberculosis, predominantly right-sided. She had no signs or symptoms of tracheobronchial disease, and was not bronchoscoped.

Indirect laryngoscopic examination: September 18, 1930 (W. L. Bonham (10)): The larynx was negative. A split-pea-sized exuding ulcer was seen in the anterior tracheal wall, 5 cm. below the glottis. On October 16, 1930, the examination was repeated. The ulcer was present but was less extensive than before.

Discussion: This patient was included in the series because, while no bronchoscopy was performed, she had active pulmonary tuberculosis, and the ulcer was morphologically similar to tuberculous ulcers seen bronchoscopically. It is probable that the ulcer was tuberculous, and it is therefore included.

The patient eventually died of tuberculosis at the Jackson County Sanatorium, Jackson, Michigan.

Case 12 (252,404): G. A., a white male of 26, was first seen in 1930, when he gave a history of recurring haemoptyses, varying from 2 cc. to ¼ cupful at a time, over a period of two years. He had lost some weight. Tubercle bacilli had never been found in his sputum, although there had been numerous examinations. Roentgenograms with and without lipiodol instillation showed no evidence of either pulmonary tuberculosis or bronchiectasis. There was a calcified lymph node in the right hilum.

First bronchoscopy: November 10, 1930 (W. L. Bonham (10)): There was slight reddening of the right stem-bronchus. No ulcerations, erosions or broncholiths were seen and no bleeding points were encountered. All of the lobar branches were visualized and were negative. The larynx was entirely negative.

The patient returned home following the bronchoscopy. He developed a slight dry cough but there was no sputum. On three occasions there were haemoptyses.

Second bronchoscopy: March 19, 1931 (H. P. Nelson (9)): There was some congestion of the right stem-bronchus. Just inside the mouth of the left upper-lobe bronchus, there was a small ulcer, measuring about 3 mm. by 2 mm., with its long axis running around the circumference of the bronchus. The base consisted of a yellow slough. The margins were pale, and were not undermined or everted. The appearance was that of a small tuberculous ulcer. It was not possible to remove the slough from the base by rubbing it with a swab, and the procedure did not produce an abnormal amount of bleeding. The ulcer was believed to be tuberculous in origin.

Following the bronchoscopy the patient raised purulent blood-tinged sputum for a few weeks but had no haemoptyses.

In March, 1932, the patient was admitted to the Michigan State Sanatorium,

where roentgenograms showed a moderately advanced, right-sided pulmonary tuberculosis. Pneumothorax was induced. At the present time the patient has bilateral pneumothorax because of bilateral tuberculosis. Another bronchoscopy was performed because of recent intermittent haemoptyses. Sputum has been negative for one year.

Bronchoscopy: October 26, 1935 (Paul C. Samson (9)): There were practically no secretions. The lumen of the right middle-lobe bronchus was slightly reduced just beyond its orifice. An excellent full-lumen image of the left upper-lobe orifice was obtained. The previously described ulcer had healed, and the submucosal defect with slightly elevated fine striae of scar-tissue was plainly visible. There was no stenosis. Nothing was seen in the tracheobronchial tree which could account for the haemoptyses.

Discussion: The patient was bronchoscoped because of unexplained haemoptyses. At the time the ulcer was discovered, physical examination, roentgenological and laboratory examinations were all entirely negative for pulmonary tuberculosis. Whatever the source of the tuberculous ulcer it is known to have preceded any demonstrable parenchymal infiltration; in this respect the case is unusual. It is possible that a bronchial lymph node ulcerated through the mucosa and has remained the active focus of the tuberculosis which eventually invaded the parenchyma of both lungs. The recent bronchoscopy presents further evidence of the healing of ulcerative lesions without stenosis.

A summary of the 12 patients included in this group shows that at present four are dead, three as a direct result of their tracheobronchial disease (cases 1, 3, 4, 11); three are clinically and bronchoscopically unimproved (cases 2, 5, 7); and five show improvement by bronchoscopic examination, although none is well (cases 6, 8, 9, 10, 12).

In the next group of patients, six in number, the tracheobronchial lesions found on bronchoscopic examination were considered to be those of early tuberculosis of the trachea or bronchi. All were nonulcerative and nonstenotic.

Nonulcerative and Nonstenotic Tuberculous Tracheobronchitis

Case 13 (263,680): P. I., a white male of 21, was first seen in the summer of 1931. Previously there had been a two-year vague history of cough with productive sputum and fatigue. There was slight pleuritic pain. One year previously positive sputum had been found at the Morgan Heights Sanatorium, Marquette, Michigan, but there were no definite roentgenological findings in the pulmonary parenchyma at that time. Roentgenograms on admission showed a slight increase in the peritruncal markings of the right base. Two months previously there had been an haemoptysis, and at times an irregular,

intermittent fever of 99.6°F. or slightly above. Mediastinal lymph nodes apparently showed in the lateral film. The patient was bronchoscoped because of a presumptive diagnosis of tuberculosis without demonstrable parenchymal lesion.

Bronchoscopy: July 10, 1931 (H. P. Nelson (9)): The mucosa of the inferior portion of the right lower lobe bronchus was definitely abnormal. Multiple capillaries could be seen. The condition extended into one of the tertiary branches. Here, small white gelatinous nodules projected from the surface of the bronchus. The left bronchial tree was entirely normal. The nodules were considered to be submucosal tubercles. The impression was that of a bronchial tuberculosis of the right lower-lobe bronchus.

Following bronchoscopy there were more frequent elevations of pulse and temperature, and the sputum was temporarily increased in amount and became highly positive for acid-fast bacilli. The patient returned to the Michigan State Sanatorium and a right phrenic paralysis was produced on May 3, 1932. He was discharged on June 27, 1932, as an apparently arrested case of minimal tuberculosis. In March, 1934, he developed frank symptoms of pulmonary tuberculosis with haemoptysis and was admitted to the Michigan State Sanatorium on October 16, 1934, with a diagnosis of bilateral far-advanced pulmonary tuberculosis with left-sided cavitation. A left pneumothorax was induced on October 20, 1934. At present his sputum is negative, but he has recently developed a tuberculous empyema on the side of the pneumothorax.

Discussion: This case is of importance because of the presence of a nonulcerative tuberculous bronchial lesion, without definite roentgenological evidence of pulmonary tuberculosis and because of the later development of parenchymal tuberculosis (compare case 12). Since enlarged mediastinal lymph nodes were demonstrated roentgenologically these must be at least considered as possible foci from which the bronchial mucosa was involved with tuberculosis either by submucosal lymphatic extension or by direct ulceration at some point not seen bronchoscopically.

Case 14 (308,338): F. M., a white male of 25, had pulmonary tuberculosis for five years, and numerous collapse-therapy measures were instituted, including phrenic-paralysis operations, bilateral pneumothorax, and finally a three-stage, nine-rib thoracoplasty with the addition of an anterior stage. He returned to the hospital for consideration of a secondary thoracoplasty because of persistently positive sputum, 30–50 cc. in amount daily. Frontal and oblique roentgenograms failed to show a definite excavation. There were no clinical symptoms of tracheobronchial disease. The larynx showed chronic catarrhal laryngitis on several occasions, both before and after bronchoscopy.

Bronchoscopy: February 16, 1935 (Cameron Haight (9)): A 2-3-mm. submucosal tubercle was located in the midportion of the carina, causing a definite

bulging of the carinal spur, but there was no ulceration. A similar, but smaller, tubercle was present in the distal and anterior portion of the mouth of the right upper-lobe bronchus. A third tubercle was present on the lateral wall of the stem-bronchus, midway between the upper- and middle-lobe orifices. A small amount of oedematous granulation tissue was present on the anteromesial wall of the middle-lobe bronchus. The granulation tissue did not reduce the lumen of this bronchus to an appreciable degree. The upper-lobe orifice was widely patent, without ulceration or stenosis. The left side was entirely normal, aside from mild injection. No demonstrable tracheobronchial disease was found today to account for the positive sputum, other than possibly the granulations in the middle-lobe bronchus.

This patient had a secondary thoracoplasty in two stages. The sputum remained from 20 to 40 cc. and had approximately the same consistency as before the operation. It has recently become negative for acid-fast bacilli on concentrate examination.

Discussion: This patient has been considered as an early case of tuberculous tracheobronchitis. The rôle that early tracheobronchial lesions play in the persistence of positive sputum is problematical. It was felt that the granulation tissue might be the source of the positive sputum. We hope to bronchoscope this patient again to determine the status of the lesions described above.

Case 15 (320,013): V. W., a white female of 46, was seen in the Department of Otolaryngology in August, 1933, because of wheezing and coughing. At that time, infiltration and ragged ulceration of the interarytenoid folds were found: tuberculosis was suspected. For this reason a roentgenogram of the chest was made and a moderately advanced bilateral apical pulmonary tuberculosis was diagnosed. In June, 1934, a right temporary phrenic operation was performed with an increase and then a decrease in the amount of sputum. The wheezing continued and the sputum remained persistently positive. The laryngeal ulceration regressed.

First bronchoscopy: October 4, 1934 (Cameron Haight (9)): The mucosa of the right stem-bronchus was somewhat granular and greatly inflamed, and bled easily. At the level of, and just below, the orifice of the right upper-lobe bronchus, there were several small yellowish projections or tubercles about 1 mm. in height. There was no evidence of stenosis and the right upper-lobe bronchus was widely patent. The diagnosis was early tuberculous tracheobronchitis without ulceration or stenosis.

The patient returned to the Jackson County Sanatorium and the sputum was found to be positive on several occasions. Roentgenograms made after the functional return of the right diaphragm revealed no definite evidence of cavitation on either side although one area on the right was suspicious. For this reason a secondary phrenic-nerve interruption was done on the right side.

The sputum continued intermittently positive and the patient continued to wheeze.

Second bronchoscopy: August 21, 1935 (Paul C. Samson (9)): About two inches above the carina the mucosa on the right posterolateral wall of the trachea was injected and oedematous, and bled easily. The right side of the carina bulged inward as from extrinsic pressure, narrowing the orifice of the right stem-bronchus. The mucosal oedema and submucosal infiltration extended just distal to the middle-lobe orifice. The mucosa shrank well with the application of cocaine-adrenalin solution and assumed a granular appearance after shrinkage. No definite ulceration was seen. The process was apparently somewhat more extensive than at the time of the previous examination.

Discussion: The source of this patient's positive sputum is unknown. One possibility is the presence of minute tuberculous ulcers in the mucosa, too small to be identified through the bronchoscope. This case is one of the only two in the series in which a narrowing of the stem bronchus was apparently due to enlarged peribronchial lymph nodes (compare case 4).

Case 16 (342,807): F. T., a white female of 27, had a long history of tuberculosis. She was referred to the University Hospital for thoracoplasty because of a huge cavity in the right lung. There was marked fibrosis with retraction of the heart into the right chest. There was a wheeze which at times nearly disappeared after coughing. Coarse rhonchi could be heard over the midportion of the chest anteriorly when the wheeze was present. There was slight difficulty in raising the sputum and there had been attacks of dyspnoea without definite cyanosis. The sputum averaged 125 cc. daily; there was no great variation in amount from day to day.

Bronchoscopy: August 22, 1934 (John Alexander (9)): Both stem-bronchi were covered with sticky secretions which were aspirated. The mucosa of the stem-bronchi, but not of the trachea, was swollen and in places reddened, but there was no visible ulceration. This suggested an early phase of tuberculous tracheobronchitis, but was not sufficiently definite to contraindicate thoracoplasty. Prebronchoscopic and postbronchoscopic laryngeal examinations on August 17 and October 11, 1934, respectively, showed injection of the arytenoids with infiltration of the posterior commissure, but no ulceration.

Following bronchoscopy the patient had a three-stage eight-rib posterolateral thoracoplasty, an anterior stage, and a right permanent phrenic-nerve paralysis. Following the first stage of the thoracoplasty, she had considerable, though temporary, difficulty in raising sputum.

At present she still wheezes considerably, occasionally has some "tickling" in her throat, and is dyspnoeic on exertion. The patient was discharged with a vital capacity of less than 900 cc.

Discussion: This patient presented a tracheobronchial reaction which was

very suspicious of tuberculous tracheobronchitis. She also had the suggestive clinical signs of wheezing and dyspnoea. In evaluating such signs in this case, it should be pointed out that the increased fibrosis, manifested by dextrocardia, may have caused enough torsion of the tracheobronchial tree to result in wheezing.

As far as the bronchoscopy is concerned, the mucosa showed definite alterations in character, and a strong suspicion must be raised that an early bronchial involvement was present, perhaps a diffuse inflammatory reaction with early focal areas of specific infection, submucosal in origin. This patient should, if possible, be bronchoscoped at a later time in order to determine what course such a lesion may take.

Case 17 (347,019): J. L., a white female of 34, had a far-advanced bilateral pulmonary tuberculosis with a large left-sided cavity. She had some respiratory wheezing and, in the early part of her sanatorium history, there were an erratic temperature and pulse. Anatomically, she presented an indication for left thoracoplasty.

Bronchoscopy: October 26, 1934 (John Alexander (9)): The lumen of the left stem-bronchus was considerably less than normal; the mucosa was swollen, irregular in places, granular, and was more suggestive of submucosal proliferation than of ulceration. No tubercles were seen. The mucosa shrank well on the application of 10 per cent cocaine. The diagnosis was a moderate degree of mucosal tuberculosis of the left stem-bronchus. The lesion did not definitely contraindicate thoracoplasty.

Two weeks later a four-stage, eight-rib posterolateral and anterior thoracoplasty was begun without marked postoperative reaction. The patient was discharged with negative sputum, averaging 5–10 cc. in amount; before thoracoplasty the sputum had been positive and from 50–80 cc.

This patient is at the Michigan State Sanatorium. Because of the evidence of moderately-advanced tuberculous bronchitis, her follow-up after a suitable period of time should be instructive.

Case 18 (340,575): D. H., a white female of 26, had an insidious onset of her disease in 1928, with night-sweats, afternoon fever and loss of weight, following pneumonia and pleurisy with effusion. Roentgenograms showed far-advanced bilateral tuberculosis, predominantly right-sided, with cavitation. In December, 1933, a respiratory rumble was first noticed, following a cold. The rumble was in the right chest and was palpable both anteriorly and posteriorly. This persisted intermittently without relation to posture, and could be relieved by considerable coughing. A tuberculous tracheobronchitis was suspected clinically. There was no dyspnoea. The vital capacity was 1,200 cc. The larynx showed a chronic tuberculous involvement without ulceration. A right-sided

thoracoplasty was recommended, provided no contraindications should be found bronchoscopically.

First bronchoscopy: July 23, 1934 (John Alexander (9)): A large number of sticky secretions were found in the trachea and both stem-bronchi. The right stem-bronchus was partially obstructed by a great swelling of the mucosa and it was much reddened; there was no ulceration. The left stem-bronchus was only a little narrowed from swelling of the mucosa; no ulceration was seen. The diagnosis was extensive tracheobronchial inflammation, presumably tuberculous, without ulceration. Thoracoplasty was not then recommended because of the tuberculous tracheobronchial lesion, but was to be considered after three months of strict bed-rest.

During this time there was satisfactory clinical improvement: the sputum decreased from 40–80 cc. to 20–30 cc. but remained positive.

Second bronchoscopy: October 22, 1934 (John Alexander (9)): The mucosa of the trachea and left stem-bronchus was moderately swollen, that of the right stem-bronchus being markedly swollen. What appeared to be tiny tubercles at the one-o'clock position at the entrance of the right stem-bronchus were seen. The mucosa was everywhere somewhat reddened, but no ulceration was visible. The mucosa shrank well after the application of cocaine and adrenalin. There was no increased appearance of pus in any bronchus after the mucosa was shrunken. The impression was that of a mucosal tuberculous involvement, predominantly in the right stem-bronchus. The swelling was possibly somewhat less than when this patient was bronchoscoped three months previously.

Following bronchoscopy, it was decided tentatively to proceed with the thoracoplasty, and the patient was readmitted in January, 1934, after having shown still further clinical improvement. Laryngeal examination at that time showed slight improvement of the tuberculous involvement and no ulcerations were seen.

In the next month and a half she had a three-stage, seven-rib thoracoplasty; following the first stage she developed postoperative paradoxical movements of the thoracic wall and her condition was poor for several days. On March 25, 1935 an anterior thoracoplasty was performed and it was followed by a satisfactory convalescence. She was discharged to the Michigan State Sanatorium with negative sputum.

Discussion: In this case there was definite improvement in both the tracheobronchial and laryngeal condition upon strict bed-rest. It is of importance to note that the laryngeal lesion became better in spite of what trauma was produced by bronchoscopy. The patient should be bronchoscoped again in order to determine the behavior of her tracheobronchial lesion following thoracoplasty.

A summary of the 6 patients included in this group shows that at present

four are clinically improved following thoracoplasty. They have negative sputum and are without roentgenographic evidence of cavitation. Two are unimproved and one of these has positive sputum in spite of negative roentgenographic evidence of pulmonary cavitation. This patient had a secondary right temporary phrenic-nerve interruption. The second patient has had negative sputum since the induction of a left pneumothorax, but has recently developed a tuberculous empyema on the left side.

COMMENT

The division of the 18 patients into two groups has seemed logical because of the characters of the lesions presented, and because of the difference in prognosis. By analogy to ulcerative tuberculous lesions elsewhere in the body, tracheobronchial ulcers are apparently late and active manifestations of the disease, and probably show a decreased resistance on the part of the patient. In at least four of the patients, ulcerating lesions developed during an excellent control of the parenchymal tuberculosis. In several patients repeated bronchoscopic examinations have shown a gradual progression of the ulcerative disease. At the present time we are not in favor of major collapse-therapy measures for pulmonary tuberculosis in patients showing active ulcerating tracheal or bronchial lesions. If, however, future studies reveal either specific methods for the control of such lesions or their spontaneous retrogression without the formation of a damaging stenosis, thoracoplasty or some other type of appropriate collapse therapy may conceivably be employed for the parenchymal disease.

Because of the relatively recent recognition of tuberculous tracheobronchitis as an important clinical entity, criteria for treatment are lacking; in only two patients in this series has an attempt been made to treat an ulcerating involvement of the bronchus directly. In case 6, irradiation therapy was given for several weeks. The bronchoscopic and symptomatic improvement to date (seven months after the last treatment) has been gratifying. In case 2, repeated small subcutaneous injections of tuberculin caused no change in the symptoms referable to the patient's tracheobronchial lesions. In other patients with distressing respiratory difficulties, the symptomatic use of atropine, adrenalin, ammonium chloride and autogenous sputum vaccine caused no improvement.

Bronchoscopic evidence of the healing of ulcerating lesions has been presented (cases 3, 4, 6 and 12). As is true of ulcerating lesions else-

where, particularly in the larynx (Lederer (12)), the healing process in the trachea and bronchi is typically one of tissue deficiency, with the formation of scar-tissue and more or less diffuse fibrosis. In only one instance (case 4), in which an ulcer had been previously described, was there no evidence of ulcer or fibrosis found at necropsy. With the healing of an extensive ulceration, stenosis of varying degree may result. The persistence of distressing respiratory symptoms in several of our patients because of a stenotic lesion has proved that such healing is not necessarily beneficial. In case 3 the diffuse stenosis which resulted from the healing of the ulcerating lesion was probably the immediate cause of death.

We have not attempted to distinguish between endobronchial and peribronchial stenosis as described by Myerson. No characteristic form of stenosis of tuberculous origin has been found in our series. Eloesser (13) agrees with this, but believes that stenosis can occur from a submucosal fibrosis in the absence of mucosal ulceration. He (11) has further suggested the torsion of the larger air-passages following pneumothorax, paraffin pneumonolysis or thoracoplasty as a possible causative agent in the production of stenotic changes. No patient in our series has demonstrated this possibility.

In the second group of cases some question might be raised as to whether the mucosal changes found at bronchoscopy were actually due to tuberculous involvement. So far as is known in our series, and in those of others, there has been little correlation between bronchoscopic findings and microscopic appearance; and it is, therefore, impossible to report the exact nature of the underlying inflammatory process in cases of this type. Studies are being undertaken at present which we hope will tend to clarify this problem. It is well known, however, (Eloesser (11), Reichle and Frost (14), and Myerson) that there are forms of submucosal tuberculous involvement which may be either diffuse or relatively nodular. Grossly, the overlying mucosa in these cases shows definite changes: oedematous thickening, infiltration with loss of the normal lustre, diffuse granularity, and tubercle or tuberculoma-formation. Hyperplastic tuberculous granulation tissue may be present with or without ulceration. These changes are similar to those found in early tuberculous laryngitis. Such changes are considered indicative of early tuberculous tracheobronchial disease; they are frequently found in patients presenting symptoms of tuberculous tracheobronchitis. The bronchoscopic appearance of such lesions is markedly different from that

seen in other patients with pulmonary tuberculosis in whom the mucosa has been entirely normal or, perhaps, slightly reddened.

It was believed that the lesions found in the second group of patients represented an early and relatively less active type of tuberculous involvement than occurs in the first group and, therefore, that the prognosis might be better. Accordingly, thoracoplasties were performed on the three patients who presented the proper indications. Our experience has been too limited to foretell what effect pulmonary collapse may have on early tuberculous tracheal or bronchial disease. A certain number of patients with this type of lesion will inevitably develop ulcerative tracheobronchitis. Whether or not this number may be reduced by active pulmonary collapse can only be learned by early diagnosis and by careful bronchoscopic reëxamination after a suitable time. This study is being contemplated for the present group and will form the basis of a future report.

The safety of bronchoscopic biopsy of suspected lesions is pertinent. Myerson, and Clerf, have reported no untoward results from the taking of biopsy specimens, but careful study of their case-summaries shows that in many instances actual tuberculous tissue was not included in the biopsy. At least one of our patients (case 4) developed a persistent elevation of pulse, increased sputum and intermittent low-grade fever following bronchoscopy and biopsy. Roentgenograms taken six weeks later showed a parenchymal spread of the tuberculosis. Because of this experience we are of the opinion that biopsy in suspected tuberculous tracheobronchitis is contraindicated. If, as frequently happens, a relatively normal portion of tracheal or bronchial mucosa is removed, a fresh avenue of entrance into the mucosa is created for tubercle bacilli with the possibility of the formation of a new active focus. If the tuberculous lesion itself is biopsied, there is danger of pulmonary parenchymal or generalized miliary spread because of the probability that the natural defensive barriers of the body will have been abruptly broken. The partial removal of tuberculous tissue elsewhere in the body often leads to persistent tuberculous sinuses; in the trachea and bronchi there is the added hazard of pulmonary dissemination.

Laryngeal examinations in the 18 patients showed that in ten the larynx was entirely negative. Ulcerating lesions were described in only four patients, and in three of these the ulcers had healed before discharge. In the 4 patients with the most advanced ulcerative and stenotic tuberculous tracheobronchitis, three of whom subsequently died, the larynx was

entirely negative at the time that the original diagnosis of tracheobronchial disease was made. These observations appear to refute Lederer's statement that tracheal involvement is usually secondary to tuberculous laryngitis.

In agreement, however, with Lederer's age-incidence figures for tuberculous laryngitis, our patients with tracheobronchitis were almost all between the ages of twenty and forty. Only two patients were more than forty years of age and none was under twenty. The submucosal infiltrative type of tuberculous laryngitis does not appear to contraindicate bronchoscopy, since, in those patients in which prebronchoscopic and postbronchoscopic examinations of the larynx were made, there was no demonstrable increase in the laryngeal lesions. If, however, definite laryngeal ulceration exists, particularly on the vocal cords, posterior commisures or aryepiglottic folds, we believe that bronchoscopy should not be done until all evidence of ulceration has disappeared, since we feel that ulceration is indicative of more active disease than is submucosal infiltration.

Eloesser (11), Betke (15), and Bucher (16) have cited instances in children in whom enlarged tuberculous tracheobronchial lymph nodes caused obstruction to breathing, or actually ulcerated through the walls of the larger air-passages with resulting suffocation. Only two of our patients, cases 4 and 5, had obstruction of this type which caused symptoms. In the former, the true nature of the obstruction was not recognized until necropsy. Myerson likewise reports the infrequent occurrence of this condition in adults.

SUMMARY AND CONCLUSIONS

1. Since bronchoscopy is a determining factor in establishing a diagnosis of tuberculous tracheobronchitis, repeated bronchoscopic examinations are valuable to determine the progression or regression of lesions. In this clinic such observations have determined to a large extent what type of collapse therapy, if any, should be employed for the pulmonary tuberculosis. A group of 18 patients, comprising 12 females and 6 males has been presented, in whom a bronchoscopic or laryngoscopic diagnosis of tuberculous tracheobronchitis was made. Because of the definite symptom-complex which they presented, a prebronchoscopic clinical diagnosis of this disease was made in 12 patients and confirmed in eleven by bronchoscopic examination.

2. Twelve of the 18 patients had ulcerating or stenotic lesions, or both.

In at least four of twelve the tracheobronchial lesions apparently developed while the parenchymal disease was under control. At present four of the twelve are dead, three are clinically unimproved and five show some improvement in their tuberculous tracheobronchitis. Evidence of the healing of ulcerative lesions by fibrosis, in many instances leading to stenosis, has been presented. This form of healing has been shown to be not necessarily beneficial to the patient. Major collapse therapy for pulmonary tuberculosis is at present not used when ulcerative lesions are discovered, in view of their poor prognosis. In one case, irradiation therapy directed at the tracheobronchial lesion has apparently caused improvement.

3. The remaining 6 patients have shown sufficiently definite alteration of the tracheobronchial mucosa to be considered as early cases of tuberculous tracheobronchitis. In these patients the mucosa showed varying combinations of oedema, submucosal infiltration, mucosal granularity or definite submucosal tubercles or tuberculomata. These lesions are believed to be relatively less active than the ulcerating type and, therefore, to have a better prognosis. For this reason thoracoplasty has been employed in 4 cases for the parenchymal disease. These patients are improving at present, all having a negative sputum.

4. Bronchoscopic biopsy in suspected tuberculous lesions is believed to be contraindicated because of the danger of a miliary or of a parenchymal spread of the tuberculosis from uncovering new avenues of dissemination in the tracheal or bronchial tuberculous lesion.

The author acknowledges his indebtedness to Doctor A. C. Furstenberg, Professor of Otolaryngology, University of Michigan, for his permission to incorporate in this paper the results of bronchoscopic examinations made by members of his department, and to Doctor R. S. Anderson, Michigan State Sanatorium, Howell, Michigan, for his continued interest and his valuable clinical and diagnostic contributions. The author is grateful to Doctor G. L. Leslie and the Staff members of the Michigan State Sanatorium, and to Doctor Roger Hanna, Jackson County Sanatorium, Jackson, Michigan, for their hearty coöperation in follow-up studies. Patients were referred through the courtesy of each of the following men: Doctor F. L. S. Reynolds, Grand View Hospital, Ironwood, Michigan; Doctor J. W. Towey, Pinecrest Sanatorium, Powers, Michigan; Doctor Salvatore Lojacono, Morgan Heights Sanatorium, Marquette, Michigan.

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ANTHRACOSILICOSIS AND TUBERCULOSIS[1,2]

MARTIN J. SOKOLOFF

The development of tuberculosis in the pneumonoconiotic lung depends, to a great extent, upon the chemical composition of the dust to which the individual has been exposed. It has been known for many years that tuberculosis is comparatively uncommon in workers exposed for prolonged periods to the non-silicon-containing dusts, such as carbon, lime and marble. On the other hand, metal-miners, tile-makers, granite-cutters and others, who work in an atmosphere heavily laden with silica particles, are particularly susceptible to tuberculous infection.

Of all the varieties of inorganic dusts capable of producing changes in the lungs, that arising from coal is the only one to which is attributed the property of inhibiting the development of tuberculosis. The exact way in which carbon exerts this protective action is unknown. Crocq (1), who in 1862 called attention to the high resistance of coal-miners to tuberculosis, thought that carbon was harmless to the lungs and exerted an atrophic effect on tubercles. Wedekind (2) believed that coal dust stimulates the reticuloendothelial cells and increases phagocytosis. Cummins (3) showed that the finely powdered dust of anthracite coal is capable of adsorbing a large portion of the active principle from diluted Old Tuberculin, and concluded that the protective influence of carbon is due to its power to adsorb the products of growth and destruction of tubercle bacilli.

In contradistinction to this protective character of carbon dust is the injurious effect of silica dust. Prolonged inhalation of silica increases the susceptibility to tuberculosis to such a degree that Gardner (4) has estimated that at least 75 per cent of human beings who develop silicosis die of tuberculosis. Various theories have been offered in explanation of this phenomenon. Gye and Kettle (5) considered silica an active cell poison, which favored the development of tuberculosis by causing necro-

[1] From the White Haven Sanatorium, White Haven, Pennsylvania, and the Department for Diseases of the Chest, Jefferson Hospital, Philadelphia, Pennsylvania.

[2] Read at a meeting of the Eastern Section, American Sanatorium Association, Rochester, New York, October 5, 1935.

sis of the tissues. They thought that the coagulum which formed as a result of this necrosis afforded mechanical protection to the tubercle bacillus and acted as a medium favorable for its growth. Gardner (6) found, by animal experimentation, that the inhalation of dust (quartz, carborundum, granite) stimulated multiplication of bacilli in healing tubercles. He suggested that the action of the siliceous dust, in lighting up preëxisting foci of infection, might be responsible for the frequent association of silicosis and tuberculosis.

FREQUENCY OF INFECTION

In view of the inhibitive effect of carbon upon the development of tuberculosis it seems reasonable to believe that pulmonary tuberculosis should be uncommon in coal miners. Indeed, early observers were unanimous in their opinion that this was the case. The survey made by Wainwright and Nichols (7) in 1905 is typical. These investigators, studying the effect produced by coal-dust upon a large group of miners in Pennsylvania, concluded from their data that tuberculosis was about two-thirds less frequent among these men than among all other employed males. During recent years, however, pulmonary tuberculosis in coal miners has been seen with increasing frequency. In 1932, Kibbey (8), of Alabama, reported that coal-miners die from tuberculosis with nearly three times the frequency of the average for the total population and have a mortality rate more than two and one-half times that of surface mine-workers. In addition, Enid Williams (9) of Wales (1933) reported the results of her studies upon a group of 100 old and retired coal-miners. In 6 of them tubercle bacilli were found in the sputum on the first examination. In 28 of the remaining 94, other signs suggestive of tuberculosis were found. Williams ventured the opinion that there is a higher degree of tuberculosis among coal-miners than the older statistics seem to indicate.

CHANGED WORKING CONDITIONS IN COAL-MINES

An investigation of the conditions under which modern miners work may explain the discrepancy between the older and more recent surveys.

The chief hazard in mining is the dust produced by drilling. Before the institution of modern methods in the coal-mining industry hand-drills were used exclusively. In order to avoid the hard rock, most of the drilling was done directly into the coal along the edge of the vein. This was a slow and laborious procedure, but the dust generated by these drills

consisted of rather large particles which, as a rule, settled quickly. Since the removal of the small veins required an extensive amount of drilling they were left undisturbed whenever feasible. Thus the coal-miner of this period was exposed to dust which consisted almost entirely of carbon and, because the constituent particles were large and coarse, symptoms of extensive pneumonoconiosis usually did not appear before exposure of from 12 to 15 years.

The hand-drill has gradually been replaced by the dry pneumatic drill or "jackhammer." This instrument creates a dust consisting of fine particles, which at times is blown back with great force directly into the face of the operator. This dust remains suspended in the air many hours after drilling has ceased. As a result of the inhalation of this fine and highly concentrated dust, symptoms of severe respiratory impairment may appear after a period of exposure of only 3 or 4 years.

The pneumatic drill has simplified and expedited separation of small veins of coal which, under the old method, were considered too insignificant and too time-consuming for removal. A tremendous amount of drilling is necessary to reach these small veins and most of it must be done directly into rock. The present day coal-miner, therefore, spends a considerable part of his time in rock-drilling which adds to the hazard of his occupation by creating an atmosphere laden with a great amount of fine silica particles in addition to the usual amount of coal-dust. Analyses of the dust of anthracite coal mines in Pennsylvania, made by Brundage and Frazier (10), of the U. S. Public Health Service, show that at times the concentration may be as high as 1 billion particles per cubic foot of air, with an average dustiness of 124 million particles per cubic foot of air, and that the dust to which certain of the workers are exposed contains as much as 31 per cent of free silica. Because the miners are exposed to a mixture of two dusts, carbon and silica, classical anthracosis, in which carbon is the sole aetiological factor, is no longer seen in these workers. In support of this contention Sladden and Cummins (11) demonstrated that "The fibrosis of the lung in coal miners is always associated with silica, which in fatal cases, is present in amounts quite comparable with those found in the lungs of quartz miners in South Africa."

PURPOSE OF STUDY

In order to determine the frequency of tuberculosis as a complication of anthracosilicosis and to establish criteria by which this complication might be recognized, observations were made upon a group of anthracite

coal-miners, institutionalized because of disabling chronic pulmonary disease. To ensure proper evaluation of treatment results, only those patients who remained under treatment for two months or more were included in this study. This time-limit is necessary because the detection of this variety of tuberculosis often requires prolonged observation.

STATISTICAL DATA

The group consisted of 418 men, varying from 21 years to 67 years of age, and whose period of exposure to mine-dust ranged from 3 to 50 years.

TABLE 1

Diagnosis in 418 coal-miners with disabling chronic pulmonary disease

	NUMBER	PER CENT
Anthracosilicosis	174	41.6
Anthracosilicosis plus tuberculosis	237	56.7
Anthracosilicosis plus carcinoma	3	0.72
Anthracosilicosis plus bronchiectasis	2	0.48
Anthracosilicosis plus abscess	1	0.24
Anthracosilicosis plus gangrene	1	0.24

TABLE 2

Age-incidence of anthracosilicosis and tuberculosis in 237 patients

AGE	NUMBER	PER CENT
years		
21–30	19	8.
31–40	69	29.1
41–50	118	49.8
51–60	29	12.2
61–70	2	.8

The average age was 42.9 years and the average exposure period was 19.2 years. All of these men had used the "jackhammer" periodically. Surface mine-workers are not included in this study.

In 174 (41.6 per cent) of these patients the pulmonary lesions resulted solely from the action of mine-dust (table 1). Since extensive changes were present in all of these men, they were classified as third-stage anthracosilicosis.

Nontuberculous pulmonary complications occurred in 7 patients (1.7 per cent), carcinoma in three, bronchiectasis in two, abscess in one and diffuse pulmonary gangrene in one.

In 237 (56.7 per cent) evidence of coexisting tuberculosis was found.

In 203 of these 237 patients diagnosis was based upon the discovery of tubercle bacilli in the sputum, while in the remaining 34 patients sufficient other signs were present to warrant their inclusion under this classification.

The age-incidence of the patients with combined anthracosilicosis and tuberculosis is shown in table 2. Tuberculosis appears later in life among these workers than it does among the general population. One hundred and eighteen (49.8 per cent) were between 41 and 50 years of age, while only eighteen (8 per cent) were in the 21-to-30-year group.

The incidence of tuberculosis varied directly with the amount of dust present in the lung, increasing as the degree of pneumonoconiosis advanced. Of the 237 tuberculous cases, 13 (5.4 per cent) were associated with first-stage pneumonoconiosis, 58 (24.5 per cent) with second-stage, and 166 (70.1 per cent) with third-stage changes.

PATHOLOGICAL CHANGES

The type of tuberculosis which occurs as a complication of anthracosilicosis differs materially from that which is usually seen. It does not extend progressively downward from the apical or subapical region, but is found scattered throughout the lungs among the silicotic nodules. The tuberculous lesion is usually of slow evolution, is always present in both lungs and consists mainly of caseous nodules varying in size from a split-pea to a walnut. Tendency towards cavitation is great, demonstrable cavities being found in 43 per cent of the patients. The excavations may attain tremendous size, sometimes occupying almost an entire lobe. They are often multiple and may occur anywhere in the lungs, but the larger ones are usually found in the upper lobes. Caseous pneumonia occurs as a terminal event in many instances. Extensive plastic changes in the pleura are nearly always associated. Effusion occurs infrequently.

Since there is no way of clinically or roentgenologically determining what proportion of the change in the lungs is due to tuberculosis, division into the usual groupings of minimal, moderately advanced and far-advanced tuberculosis is impossible.

CLINICAL MANIFESTATIONS

When anthracosilicosis and tuberculosis coexist, the clinical picture assumes one of two distinct forms:—either a nontoxic or a toxic form. The former is characterized by a protracted afebrile course and by the absence

of toxic manifestations. The patients present the usual symptoms of extensive pneumonoconiosis,—dyspnoea, cough, expectoration and chest pains. In the few instances manifesting an afternoon elevation of temperature, the rise is usually less than one degree. There is only a slight impairment in general health and nonpulmonary tuberculous complications are infrequent. Because of the absence of constitutional symptoms these cases are usually considered simple anthracosilicosis, until attention is called to the tuberculosis by the discovery of tubercle bacilli in the sputum or by roentgen-ray evidence.

The second or toxic form is characterized by extensive cavitation, the clinical picture being that of rapidly progressing tuberculosis. In addition to the local symptoms, there is always severe constitutional disturbance as evidenced by fever, loss of weight, loss of appetite, weakness and profuse sweating. Fever is a predominant feature of this form. It is present throughout the entire course of the disease and is septic in type, the afternoon temperature reaching 103° or 104°F. in the majority of patients. Repeated and profuse haemoptyses occur in many instances. In this variety of anthracosilicotic tuberculosis, nonpulmonary tuberculous complications are common.

DIAGNOSIS

The diagnosis of uncomplicated anthracosilicosis presents no special problem but to determine whether or not tuberculosis coexists is very often a difficult task.

The following points are important in determining the presence of tuberculous lesions:

1: In the majority of cases if tuberculosis is present tubercle bacilli will be found in the sputum. The importance of repeated sputum examinations both of the whole and concentrated specimen must be emphasized. If consistently negative, study of the sputum by culture and guinea-pig inoculations should also be made. A characteristic feature, in some patients, is the tendency for the bacilli to be found in the sputum in showers, being present for a few days, then disappearing, only to reappear after a lapse of weeks or months. In others, bacilli are found in the sputum only once or twice in the course of a great number of analyses (figure 1). Often one hesitates to accept such reports in the belief that some error has been made in the laboratory, but such findings have been repeatedly confirmed by postmortem examination. Even if the sputum is consistently negative tuberculosis cannot be excluded. It is not

unusual to find extensive tuberculous involvement with cavity-formation, at necropsy, in individuals in whom, during life, repeated examinations of the sputum failed to reveal tubercle bacilli (figure 2).

2: Serial roentgenological studies are of the utmost importance in detecting the presence of tuberculous lesions occurring as a complication of anthracosilicosis. Roentgenographic identification of this variety of tuberculosis becomes increasingly difficult as the amount of dust in the lung increases. In first-stage anthracosilicosis, before the changes due to dust have extended towards the periphery of the lung, tuberculous

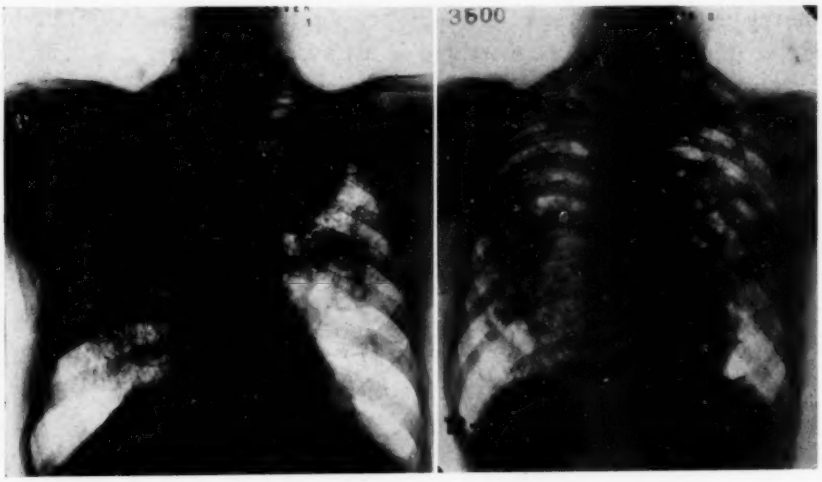

Fig. 1 Fig. 2

Fig. 1. Coal-miner, 57 years of age, exposed for 24 years. Anthracosilicosis and tuberculosis. Tubercle bacilli found in sputum on first examination; 29 succeeding examinations were negative. *Necropsy:* Immense cavity in right upper lobe and cavity in centre of middle lobe.

Fig. 2. Coal-miner, 49 years of age, exposed for 34 years. Anthracosilicosis and tuberculosis. Sixty-three examinations of sputum made over a period of 29 months failed to show tubercle bacilli. *Necropsy:* Cavity, 6 cm. in diameter, found in right upper lobe. Material scraped from lining of cavity-wall contained tubercle bacilli.

lesions may be recognized by their usual characteristics. Identification can be made with less assurance in the second stage, while in the third stage it is often impossible. The presence of cavities, particularly if they are large and bilateral is indicative of tuberculosis. In the absence of cavity-formation recognition of concurrent infection is exceedingly difficult. Asymmetrical spread of the lesions, as shown on serial roentgenograms, usually indicates the presence of tuberculosis. The observa-

tions of Pancoast and Pendergrass (12) are noteworthy. These investigators believe that in advanced pneumonoconiosis the existence of tuberculosis may be assumed if the lesion is peripherally located, if there is displacement of the trachea or hilum, or if the nodules instead of being circumscribed and regular in outline take on a hazy or irregular appearance.

3: Preponderance of constitutional symptoms, particularly when accompanied by manifestations of severe toxaemia, points to associated tuberculosis. Rapid decline in weight, extreme weakness, night-sweats and marked febrile reactions rarely occur in uncomplicated anthracosilicosis.

4: Physical examination, although often productive of vague and indistinct signs, may occasionally reveal the presence of complicating infection. If the pulmonary changes due to dust are slight, dulness, prolongation of expiration and râles elicited over the upper part of the chest are significant. In advanced pneumonoconiosis, râles may be absent in spite of extensive tuberculous change. Crackling râles heard after cough or coarse bubbling râles heard on quiet breathing usually indicate tuberculosis. When cavities sufficiently large to be identified by physical signs are present, it may be assumed, with a fair degree of certainty, that they are tuberculous in origin, provided abscess can be excluded. Cavities may occur in uncomplicated pneumonoconiosis, as a result of devascularization and necrosis, but they are rarely, if ever, large enough to be recognized by physical signs.

5: Frank haemoptysis, particularly if recurrent, suggests tuberculosis. In simple pneumonoconiosis, pulmonary haemorrhage occurs infrequently, and the bleeding is usually small in amount.

6: If pleural effusion is present and pulmonary neoplasm and heart disease can be excluded tuberculosis should be suspected. In the 174 patients with uncomplicated anthracosilicosis in this series, no evidence of pleural effusion was found. Of the 237 patients with anthracosilicotic tuberculosis 8 (3.3 per cent) developed effusion.

7: If concomitant signs of tuberculosis are found in other organs, it is reasonable to assume that it is also present in the lungs, not only because of the vulnerability of the lungs to the tubercle bacillus but, also, because their susceptibility is enhanced by the presence of silica. Lesions of bones, peritoneum and epididymis were found most frequently in this series. A rather odd finding was the relative infrequency of tuberculous lesions of the larynx.

PROGNOSIS

It is obvious that the pulmonary changes which occur as a result of the inhalation of dust are permanent and cannot be altered in any way by therapeutic measures. In many patients, however, lessening of the severity of local symptoms and improvement in general health may be obtained by a prolonged period of rest in a suitable environment. In advanced pneumonoconiosis, this improvement may be only temporary, as death often ensues as a result of acute intercurrent respiratory infections or of myocardial insufficiency. The addition of tuberculosis contributes immeasurably to the gravity of the prognosis. When this combination is present in the nontoxic form the patient may live for years in comparative comfort. In those in whom the toxic variety of combined anthracosilicosis and tuberculosis develops, a fatal termination may occur in a relatively short time.

TABLE 3

End-results in 411 patients with anthracosilicosis with and without tuberculosis

	NUMBER OF PATIENTS	IMPROVED		UNIMPROVED		DIED	
		Number	Per cent	Number	Per cent	Number	Per cent
Anthracosilicosis	174	109	62.6	43	24.7	22	12.6
Anthracosilicosis plus tuberculosis	237	57	24.1	79	33.3	101	42.6

The end-results of treatment of the patients with uncomplicated anthracosilicosis as compared with those in whom both anthracosilicosis and tuberculosis were found are shown in table 3. Some improvement was noted in 62.6 per cent of those with uncomplicated pneumonoconiosis, while 75.9 per cent of those with associated anthracosilicosis and tuberculosis were either unimproved or died.

SUMMARY AND CONCLUSIONS

Recent statistics tend to indicate that tuberculosis occurs more frequantly in coal-miners than was formerly believed. This increase in tuberculosis is concomitant with changed working conditions in coal-mines which expose the workers not only to carbon particles but also to a tremendous amount of fine silica particles. This combination of carbon and silica produces anthracosilicosis rather than the pure anthracosis seen in the lungs of coal miners of 25 or 30 years ago.

In order to determine the incidence of tuberculosis as a complication of

anthracosilicosis and to establish criteria by which this complication might be recognized, observations were made upon a group of 418 coal-miners, institutionalized because of chronic disabling pulmonary disease.

Tuberculosis was found in more than half (56.7 per cent) of this group of miners. The majority of these cases (92 per cent) occurred after 30 years of age and in association with third-stage pneumonoconiosis (70.1 per cent).

The lesions of tuberculosis associated with anthracosilicosis are distinctive. They consist of caseous tuberculous nodules, widely scattered throughout the lungs, rather than the usual apical distribution of uncomplicated tuberculosis.

There are two clinical types of anthracosilicotic tuberculosis, the non-toxic and the toxic. In the former, symptoms of anthracosilicosis predominate, while in the latter the toxaemia of tuberculosis is the distinguishing feature.

The diagnosis of tuberculosis complicating anthracosilicosis is made by the following:

1: Discovery of tubercle bacilli in the sputum. However, extensive tuberculous disease may be present with consistently negative sputum, or occasionally the bacilli may be present in intermittent showers.
2: Serial roentgenographic studies (less valuable in advanced pneumonoconiosis).
3: Marked constitutional disturbance
4: Physical examination (not usually helpful)
5: Frank haemoptysis
6: Pleural effusion (absent in uncomplicated anthracosilicosis)
7: Tuberculosis in other organs

Tuberculosis superimposed on anthracosilicosis greatly increases the gravity of the prognosis.

It appears from this study that the statement that coal-miners have a high resistance to tuberculosis can no longer be made without qualification. The protective nature of carbon is operative only when there is a slight degree of pneumonoconiosis present. It seems that when carbon and silica are both present in the lungs in small amounts, the protection afforded by the carbon is sufficient to overcome the harmful effect of the silica, and resistance to infection by the tubercle bacillus is increased. The infrequent occurrence of tuberculosis among younger coal-miners and the fact that it is not often seen in association with first-stage anthraco-

silicosis support this theory. On the other hand, when both these dusts are present in amounts large enough to cause serious impairment of the respiratory function the action of the silica is paramount. Under these conditions the susceptibility of coal-miners' lungs to tuberculosis approaches that of individuals suffering from simple silicosis.

It is difficult to determine the frequency with which tuberculosis occurs in coal-miners as a complication of anthracosilicosis. Information obtained from a survey of the death-records is unreliable because most of the data thus obtained concerns individuals who have been treated at home. It has been shown that the detection of tuberculosis occurring coincidently with pneumonoconiosis may require prolonged observation, with repeated analyses of the sputum and serial roentgenographic study. As it is often impossible to study these patients adequately, in their own homes, it is probable that in many instances complicating tuberculosis remains unrecognized, and the diagnosis of simple pneumonoconiosis is made because of the characteristic clinical picture. Until such time as a carefully controlled survey of a large group of coal-miners is made, the exact incidence of tuberculosis among these workers must remain a matter of conjecture.

The writer is indebted to Dr. Joseph Walsh for the postmortem material discussed in this paper.

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THE COMPARATIVE MORTALITY OF PATIENTS DISCHARGED FROM TUBERCULOSIS SANATORIA[1,2]

H. E. HILLEBOE

The purpose of this review of the literature on the mortality of patients discharged from tuberculosis sanatoria is to present the post-sanatorium mortality statistics in which comparative studies have been made, using suitable control populations. This mortality experience is of practical importance to physicians, administrators, employers, insurance companies, and social-service workers who assume the responsibility of rehabilitation. Perhaps the most vitally concerned individual is the tuberculous patient himself, upon whom any increased force of mortality will be exerted.

For the acute communicable diseases, such as diphtheria, scarlet fever and measles, it is relatively simple to measure mortality because the excess risk is concentrated within a few weeks following invasion of the household, as pointed out by Frost (1). The required period of observation is brief; collation of the data is not difficult because the time-factor is practically the same for all persons in the family. The information needed for the study of tuberculosis mortality is not so easily obtained because of the slow evolution of the disease in which the risk is not limited within a short period following a known exposure. Observation of the discharged patients must extend over a period of years sufficient to define rates of mortality for successive intervals. Systematic follow-up of a large number of people over a long time is exceedingly difficult, and completeness of records is rarely attained.

In making predictions applicable to a population as a whole, it is essential that random samples of the population be taken as basic data; selected samples will tend to bias the results in the direction of the selection. It is also imperative in any comparative analysis that all

[1] From the Division of Tuberculosis, Minnesota State Board of Control, Saint Paul, Minnesota.

[2] Presented at a meeting of the Minnesota Sanatorium Association, Crookston, Minnesota, September 2, 1935.

variables be carefully noted and weighed before reliable deductions can be made.

The relative importance and influence of certain variables should be borne in mind when one evaluates mortality rates and ratios in post-sanatorium patients. The reason for admission is an important factor in the formation of the sanatorium population. Some patients are referred by private physicians; others by clinics; still others resort to the institution of their own accord because of inability to care for themselves at home. Progressive disease forces many patients to enter sanatoria in spite of their disinclination to become hospitalized. All patients diagnosed as tuberculous do not go to sanatoria; on the other hand, many nontuberculous individuals are admitted unintentionally. The distribution may vary markedly from place to place and in successive years.

The size, facilities and personnel of sanatoria differ greatly in the various states and countries. In many institutions, rest, diet, fresh air, and sunshine form the complete therapeutic armamentarium. Numerous sanatoria admit only persons of certain ages, color, race, and economic status; frequently, the extent of the disease must be limited to minimal lesions.

Uniform diagnostic standards and classification of the disease in various stages have not been universally adopted by various workers throughout the world. Until quite recently, X-ray examinations of the lungs were not used routinely at some of the institutions whose follow-up reports were studied. Since the advent of X-rays and their expert interpretation, there is greater accuracy in the diagnosis of tuberculosis and more exactness in the exclusion of nontuberculous pulmonary diseases.

The duration of treatment or residence in a sanatorium appears to be a definite factor in the after-mortality. Knight and Dublín (2), Whitney and Meyers (3), and others have investigated this point and have found it to be of importance especially in the incipient and moderately advanced cases. The number of previous hospitalizations also enters into the question. In 1934, 23 per cent of the patients admitted to Minnesota state and county sanatoria were readmissions (4). These patients would not have the same base-line to start from in their after-mortality as those admitted for the first time. Readmissions occur usually because of extension or lack of arrest of the disease.

Then comes the consideration of special treatments, such as pneumo-

thorax and other forms of chest surgery. If these procedures have a permanently curative effect and can be used on a sufficient number of patients, presumably the sanatoria employing such measures will have better results than those not using special treatments.

The condition of the patient on discharge is another major variable to be considered. It is common practice to classify the tuberculosis at time of discharge according to degree of improvement or unimprovement. The classification of the lesion (minimal, moderately, or far advanced) is not reviewed at that time, but accepted as on admission. This, however, is not always true. A patient may be far advanced on admission and by beneficial therapy may become moderately advanced and arrested on discharge.

Regarding the actual follow-up information itself, most investigators have accepted as accurate only data concerning the patient as to whether or not he is alive, dead or untraced. It is essential to be able to determine what happens to a majority of the patients who are admitted and discharged and followed-up during the period of observation. If only a small proportion of the discharged patients are traced, the figures obtained are of doubtful value in making predictions for the group as a whole. The ability to trace 25 per cent of the patients discharged does not give one the license to predict that the same rates of mortality would be experienced by the unknown and untraced 75 per cent.

From clinical experience it is reasonable to say that a person ill with pulmonary tuberculosis usually has a better prognosis and gets along better if sent to a sanatorium. Attempts to prove this statistically have been made at various times, but, to the best of my knowledge, have been uniformly unsuccessful. There is a lack of any control group in the general population from which sanatorium patients are drawn, that could be used for comparison. Such a random sample would need to be composed of tuberculous individuals not having received sanatorium care, yet who have had X-ray, sputum, and other examinations during their period of illness. The case-records of Flint, Pollock and Williams, quoted by Elderton and Perry (5), are apparently the only records available for presanatorium days. Unfortunately, the basic data from the papers of these pioneers are not set up so that comparisons can be made with some of the later works.

It is obvious, then, that we cannot determine from the data available, the apparent or real benefits of sanatorium treatment for a tuberculosis patient in terms of what one might expect with or without that treat-

ment. We can, however, get a rate of survival or the rate of death (not necessarily of tuberculosis as the only cause) for the immediate years after discharge. This, in turn, can be compared with the experience of persons of similar age, sex, etc., in the general population from which the sanatorium patients were drawn. The ratio of the actual deaths to the number of deaths that would be expected if these discharged patients had never gone to a sanatorium will give an accurate measure of the comparative mortality of patients discharged from tuberculosis sanatoria.

The force of mortality is commonly expressed as an annual death-rate; that is, the ratio of deaths to the number of people under observation for one year. This death-rate for tuberculosis varies widely with age, and accordingly should be determined separately for each age-group, if significant comparisons are to be made. The method of reducing the mortality of discharged patients to terms of age specific annual death-rates is clearly described in detail by Elderton and Perry (5) (6) and Frost (1). By converting observations on patients to terms of life experience, a unit of one person observed for one year, or one person-year, is obtained and can be used with great flexibility in comparative studies.

The following specific information concerning every patient should be known at discharge and at intervals during observation: the age; the date and cause of death (only the total death-rate is ordinarily used because reports of deaths due to tuberculosis are of questionable accuracy, unless the death-reports come from sanatoria or hospitals, which usually furnish less than 25 per cent of the returns); on what anniversary of discharge, if alive; the last known date of follow-up, if untraced. From these facts the number of person-years each person contributes to the life experience of the group becomes available as the denominator in the ratio of which the number of deaths makes up the numerator.

Although there are many comprehensive reports in the literature on the subject of postsanatorium mortality (3) (7) (8) (9) (10) (11) (12), the ones of particular interest for this review are those of Brown and Pope (13), Elderton and Perry (5) (6), Bardswell and Thompson (14), Hartley, Wingfield and Thompson (15), and Knight and Dublin (2), in which life-table methods of analysis are employed. It is to be noted that most of these studies are not of recent date, in spite of the fact that the literature was investigated rather carefully up to the middle of 1935.

In their statistical study Brown and Pope used the English life-table number three, combined males and females, and used the average age of patients for finding the expected number of deaths. The results are difficult to discuss, because the cases are subdivided according to the condition on discharge, but not according to admission classification. This study covers observations made at Adirondack Cottage Sanitarium (later Trudeau Sanatorium) in New York state as early as 1885.

In 1913 Elderton and Perry in England were forwarded the data from the Adirondack Cottage Sanitarium and analyses were made of the material. These workers based their findings on the number of years followed since admission rather than discharge.

TABLE 1

Ratio of actual to expected number of deaths from date of discharge (except Adirondack)

SANATORIUM		ADIRONDACK (SPECIAL)†	MIDHURST			BROMPTON			METROPOLITAN		
	Condition on Discharge										
Condition on Admission	Sex	Total	Arrested	Not arrested	Total	Arrested	Not arrested	Total	Improved	Not improved	Total
Group 1	Male	3.6	3.9	9.5	6.4	2.9		4.5	0.99	*	1.29
	Female	2.3	3.4	9.1	4.7	1.8		2.6	2.1	*	
Group 2	Male	10.0	5.3	18.4	16.6	7.2		16.2	4.0	19.5	5.48
	Female	10.4	5.8	22.7	19.0	7.9		15.7	3.9	46.4	
Group 3	Male	36.8	*	40.0	39.2	9.4		42.6	3.3	59.0	16.98
	Female	45.4	6.6	38.6	37.5	17.3		63.4	*	300.0	

* No actual deaths for comparison with expected.

† From date of admission.

Of the patients studied, white Americans were in the majority. Diagnoses were made without the aid of X-rays, and patients were classified into three groups,—incipient, advanced, and far advanced. Using the English life-table number six in order to get the expected number of deaths, the ratios of actual to expected deaths were, for the incipient 3.0:1; advanced, 10.2:1; and far advanced, 39.9:1 (table 1). In other words, a tuberculous patient discharged from a sanatorium with advanced tuberculosis was exposed to 10.2 times greater risk of dying than an individual of similar age and sex in the general population. Stated another way, males with incipient tuberculosis under twenty-three years of age experienced a mortality similar to sixty-three-year-old persons

in the general population; females with incipient disease under thirty-three years of age, had twenty-two years added to their present age. Discharged patients with tuberculous parents had no greater mortality, but seemed to be in younger age-groups, in which it is known that a higher mortality is experienced than in older age-groups. It was also observed that patients with tubercle bacilli in their sputum had at least twice the mortality of those with negative sputum.

The paper by Bardswell and Thompson (14) represented the experience from 1907 to 1916 at Midhurst Sanatorium in England. Only early cases were admitted to this institution and the majority were people of small means. Diagnoses were made without X-rays, and the American classification of 1910 was used. (For brevity in discussion, incipient or minimal will be symbolized as group 1, moderately advanced as group 2, and far advanced as group 3.) This classification does not differ markedly from that approved by the American Sanatorium Association at the present time. The average stay of patients was five months. Treatment consisted of rest in bed followed by graduated exercises. Only 3.5 per cent of 1,707 patients discharged could not be traced.

Mortality rates were based on years since discharge. The percentage of males and females discharged each year remained quite uniformly at 60 and 40 per cent, respectively. The mortality experience of group 1 was six times, group 2 sixteen times, and group 3 thirty-eight times that expected from the England and Wales death-rates of the general population. The male and female death-ratios were similar in groups 1 and 3, with higher ratios in the younger people in both. There was a higher percentage of females than males in group 1 whose disease was arrested on discharge. This was probably due in part to the fact that a larger proportion of females than males had negative sputum. The authors had the impression that, as a factor in after-mortality, the condition of the patient on discharge was more important than the classification of the disease on admission. It was also concluded in this study that arrest of the disease does not imply a cure, because supposedly-cured patients experienced a higher mortality than similar nontuberculous members of the general population. It was found that twice as many males as females had positive sputum, and that the mortality ratios of persons admitted and discharged with negative sputum were not different from those admitted with positive and discharged with negative sputum. The patient's condition on admission appeared to be

a more potent factor in future survivorship ratios than the fact that the patient's antecedents were tuberculous.

In 1919 Hartley, Wingfield and Thompson (15) investigated 3,400 cases discharged from Brompton Hospital Sanatorium from 1905 to 1914, of whom only 10 per cent were lost sight of the first two years. Admitted cases were carefully selected, and attempts were made to single out early cases with a favorable prognosis. A preliminary period of hospitalization and observation was given in Brompton Hospital before sanatorium treatment was started. Most of the patients were poorly-paid workers of the middle class. No X-ray examinations were used in diagnosis, reliance being placed entirely on physical and sputum examinations. The American classification of 1910 was used here, as at Midhurst. The average duration of stay was three months and twenty-five days. The average period of follow-up was 4.8 years for the males and 5.1 years for the females. No special treatment was used. The majority of patients were under 30 years of age. Of those discharged, approximately 70 per cent were males and 30 per cent females. The English life-table number 8 was used for getting comparative mortality rates.

These authors found the first two years after discharge the most critical period of mortality. Classified by admission diagnosis, the ratio of actual to expected deaths in group 1 was 4:1; in group 2, 16:1; and in group 3, 40:1 (table 1). Fifty per cent of the patients discharged as "worse" died during the first year after discharge. A negative sputum on discharge was considered the most favorable factor in prognosis. More females than males were discharged as "arrested" in each group. In group 1, 75 per cent of the cases were discharged as "arrested" and only 2 per cent as "worse." However, in group 3 only 49 per cent were discharged as "arrested" while 30 per cent were "worse." More males than females had positive sputum, both on admission and discharge. The authors were of the opinion that treatment should be continued until the sputum became free from tubercle bacilli.

The most recent paper was that of Knight and Dublin, who investigated the postsanatorium mortality of 1,448 patients discharged from 1913 to 1926 from the Metropolitan Life Insurance Company's Sanatorium at Mt. McGregor, New York. There were 946 males and 502 females. These patients were residents of the United States and Canada, and were mostly field- and office-workers employed by the company. The mortality rates of the tuberculous were compared with those of

the rest of the company's insured workers. The average stay in the sanatorium of group 1 cases was 6 months; of group 2, 10 months; and of group 3, 23 months. No other details were presented regarding selective factors.

The actual to expected death-ratios were as follows: group 1, 1.29:1; group 2, 5.48:1; group 3, 16.98:1 (table 1). It is to be noted in table 1 that males with minimal tuberculosis had practically the same actual number of deaths as the expected number, the ratio being 0.99:1, while the females in that group had a ratio of 2.09:1. The males, however, as a whole, had a higher subsequent mortality than the females.

Of the total cases discharged, 58 per cent were in group 1, 35 per cent in group 2, and 7 per cent in group 3. This distribution is quite different

TABLE 2

*Percentage of patients dead in successive years after discharge Brompton**

DURATION SINCE DISCHARGE	GROUP 1		GROUP 2		GROUP 3	
	Male	Female	Male	Female	Male	Female
year						
1st	1.6	0.4	6.7	4.4	27.8	29.1
2nd	4.4	0.4	18.5	12.5	51.8	51.6
3rd	8.1	1.2	30.1	19.6	64.8	65.9
4th	10.6	2.9	38.1	26.6	73.6	75.2
5th	12.2	5.6	43.5	32.5	78.9	78.2
6th	14.6	6.1	49.1	37.0	82.7	81.4
7th	16.4	8.4	52.6	41.7	84.8	84.3
8th	17.3	9.3	56.6	43.6	87.7	86.9

* Calculated from table 9, page 25.

from that found in the majority of state-maintained sanatoria where the group 2 and 3 cases make up approximately 75 per cent of the total. Of group 1 only 2.8 per cent were discharged as unimproved; of group 2, 15.5 per cent, and in group 3, 49.1 per cent. The authors have made some interesting observations on the effect of tuberculosis on the amount of time lost from work because of sickness disability. Almost all of the persons comprising this study were kept under medical supervision after leaving the sanatorium to return to their work.

The pertinent ratios in the papers reviewed have been summarized in table 1. Although the data from the various sources are not directly comparable, the similarity of results according to the classification of the disease is apparent. The striking differences between death-ratios of

those discharged improved in distinction to the unimproved are also to be noted. The relationship between the severity of the disease on admission and the condition of the patient on discharge gives the physi-

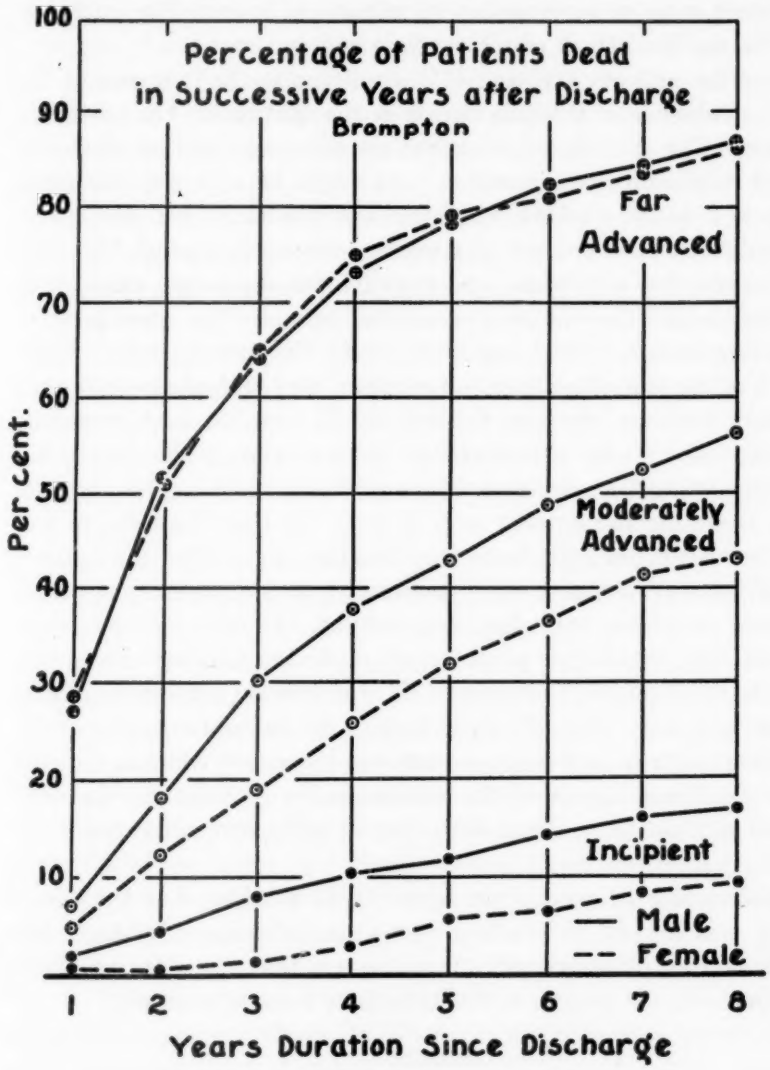

Fig. 1

cian a fairly reliable and accurate yardstick with which to measure survivorship, particularly for the immediate years after discharge.

MacSweeney (16) in 1924–1925 attempted to study, from an insurance

company medical director's viewpoint, the disability and mortality in persons with arrested tuberculosis, and met with considerable difficulty in securing measurable data. He concluded that one should be guarded in predicting rates of survivorship in relation to insurability until five years after the last attack of tuberculosis had occurred.

Some of the authors, (14) and (15), studied also the influence of the presence or absence of tubercle bacilli in the sputum on the mortality experience. The sputum examinations on admission and on discharge were both taken into consideration. As might be expected, the cases in group 1, negative on both admission and discharge, had the lowest ratios, and lower than group 1 as a whole. Strangely enough, the ratio of the positive (on admission) and negative (on discharge) cases, very nearly approached the "negative-negative" group. The cases positive on both admission and discharge had a decidedly poor outlook. These findings lend force to the clinical observation that patients treated until the sputum becomes free from tubercle bacilli have the best prognosis.

One may also study aftermortality by determining the proportion of patients dying in successive years after discharge. The common practice of stating the number or percentage who are dead one to five or ten years after discharge is of questionable value, when the number of person-years are not accurately summated, and when the proportion of untraced persons is not taken into account. In table 2 and figure 1 are shown the cumulative percentages of deaths in successive years after discharge according to classification of disease on admission. Computations were made from the basic data in the Brompton reports (15).

Attention is drawn to this simpler method of analysis which is directed towards a different aspect of the aftermortality problem, so that the procedure will not be confused with that in which mortality ratios are studied.

It is interesting to note (from figure 1), in passing, that the excess mortality was highest in the first two years following discharge, but gradually levelled off afterward. It is also true that, the more advanced the tuberculosis, the greater is the immediate force of mortality.

COMMENT

It must be definitely understood that figures on the mortality of discharged patients should not be used as a measure of results of sanatorium treatment. As previously stated, in order to evaluate the effects of treatment on patients at a tuberculosis sanatorium, one must have a comparable group of people as to sex, age, disease, etc., who have not

had sanatorium care. Such a control group is difficult to obtain, and to the best of my knowledge has not yet been made available.

However, the study of comparative mortality in discharged patients does give valid statistical proof of the soundness of many of our concepts regarding the disease. The beneficial effects of early diagnosis of serious pulmonary tuberculous lesions are reflected in the smaller risk of dying of the minimal cases in comparison to the more advanced cases during the perilous first five years after discharge. The importance of sufficient length of residence to assure arrest of the disease, particularly for patients who have been discharging tubercle bacilli in their sputum, is borne out by the pertinent mortality ratios. The urgent need for universal provision of adequate medical supervision of discharged tuberculous patients is only too obvious in view of the excessively high mortality experiences. By systematic follow-up the discharged patients who break down could be discovered and rehospitalized for further treatment or isolation. Such a procedure would not only reduce the number of unnecessary deaths, but also would result in the prevention of otherwise unavoidable tuberculous infections and disease in members of the patient's family.

Because of the fact that life-table methods of analysis have been employed very sparingly in sanatorium records in the United States, it seems appropriate to direct attention towards this method. Any sanatorium can accumulate accurate follow-up records if the few simple principles referred to are put into practice. By applying the easily mastered technique of life-table analysis to these records, and with proper regard for the variables involved, a useful mass of statistics would become available for research into the problems associated with tuberculosis mortality. The application of these methods could be extended to studies of morbidity, the effects of special treatments, socioeconomic factors, and a multiple of other fundamental questions concerning tuberculosis which remain largely unanswered.

SUMMARY

In this paper are presented life-table methods of analysis of post-sanatorium mortality statistics, in which the ratio of actual to expected deaths is used to measure the force of mortality. In the articles reviewed, which include those published from 1885 to 1935, the conclusions arrived at by the authors were as follows:

1. A person with minimal tuberculosis has his risk of dying increased approximately four times; moderately advanced, sixteen times; and

far advanced, forty times over that of persons in the general population from which the patients were drawn.

2. Females with minimal disease did not experience as high a mortality rate as males of the same class (except in the Metropolitan study); however, the females with far-advanced disease were more severely affected.

3. The age, classification of disease on admission, and condition on discharge were important variables to be considered in aftermortality.

4. The length of residence was an important factor, particularly in the minimal and moderately advanced cases.

5. The presence or absence of tubercle bacilli in the sputum on admission and discharge had a markedly noticeable effect on the aftermortality.

6. The stage of the disease on admission of the patient was a more potent factor in future survivorship than the fact that his antecedents were tuberculous.

7. The excess mortality was highest during the first two years after discharge, and increased in amount with the severity of the disease.

8. The need for more recent follow-up studies is apparent.

The writer wishes to express his gratitude to Dr. W. H. Frost, Professor of Epidemiology, Johns Hopkins School of Hygiene and Public Health, for his helpful suggestions and criticisms in the preparation of this paper.

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TUBERCULOSIS AND THE FINNS OF MARQUETTE COUNTY, MICHIGAN[1]

SALVATORE LOJACONO[2]

There is an assumption, generally accepted as fact by physicians and laymen, that Finns are especially susceptible to pulmonary tuberculosis and that they show little resistance to the disease, when infected.

Such beliefs are easily spread. They influence the community's attitude when organizing for public health, and may even affect the professional approach in the treatment of individuals.

In Michigan there are, according to the 1930 census, 74,229 foreign-born Finns and their American-born children. In the Upper Peninsula this group forms 19 per cent of the population.

It seems desirable, therefore, for us, who are interested in tuberculosis control, to have some definite knowledge of this group.

This study of tuberculosis in the Finns of Marquette County covers all cases of pulmonary tuberculosis reported in the nine-year period from July, 1926, to July, 1935. I also offer briefly some information regarding the social background of the Finnish people.

Finland lies north of Latitude 60° in a position comparable to Alaska. Its Finnish name, *Suomi*, means "swamp," and well describes the country which is a vast region of lakes, rivers and marshes. The climate is cold, with frost any month of the year, and damp, with long dark winters and 60 per cent of cloudy days.

The racial origins are uncertain, but anthropologists agree that, while the culture is Asiatic, the Finns are racially a blend. The ancient tribes settled in the Finnish peninsula before the Christian era, and 89 per cent of the present population is of pure Finnish stock. They have been under the political domination of Swedes—known here as Swede-Finns—who were probably already in possession of the fertile coastal plains, when the first Finnish tribes penetrated the interior. Since their political inde-

[1] Read at the annual meeting of the Michigan Trudeau Society at Howell, Michigan, November 1, 1935, and before the Marquette-Alger Medical Society, Marquette, Michigan, December 17, 1935.

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pendence dates only from the early part of the 19th century, national public-health measures have not been instituted until recently.

Dr. Severi Savonen, Secretary of National Association against Tuberculosis in Finland, sent me the report made by his association to the 1932 International Tuberculosis Conference, from which I quote the following:

The population in 1930 was 3,658,125 inhabitants, of which 90 per cent speak the Finnish and 10 per cent the Swedish language. Seventeen per cent of the population lives in cities; the other 83 per cent in the country. The main livelihood of the people is agriculture and cattle raising.

Births in 1930 averaged 20.6 per 1,000 and deaths 13.2 per 1,000.

The mortality from tuberculosis is high,—one of the highest in Europe. The reason for this might be that the infection is comparatively young, so that the tendency for lower death-rate, which seems to be the natural course of tuberculosis, has not taken place yet in Finland. However, the fatality in tuberculosis of the lungs was formerly still higher. At present the Society for Prevention of Tuberculosis in Finland is gathering statistics for the purpose of determining the tuberculosis fatalities beginning in 1771. These statistics show that the mortality in pulmonary tuberculosis was at its peak from 1850 to 1860. Figures were at that time double compared to present figures.

Dr. Savonen also informs me that there are in Finland 36 sanatoria for pulmonary tuberculosis; but that the death-rate was still 185 per 100,000 in 1933, as compared with an average of 232 per 100,000 from 1901 to 1911.

The Finns in America have settled in those parts of the country bearing the greatest geographical likeness to their homeland. They have concentrated in Michigan and Minnesota, Massachusetts and the Puget Sound. It is notable that Finns are largely settled in rural districts, while the general inclination for foreigners is to concentrate in urban centres.

In the Upper Peninsula of Michigan the Finn has been a steady settler since about 1870. The first group were Finns from the copper-mines of Norway who were imported by the copper mining company in Calumet.

"The absence of large mineral deposits in Finland means that few of the natives are miners. Emigration is mainly from the northerly parts of Finland where the population is scattered, and where agriculture, practically the only pursuit, is carried on under severest handicaps (1)."

In Marquette County the iron-mines have offered a ready means of earning a livelihood to the Finnish immigrant.

The other wage-earning opportunities are logging and road-making.

The Finn's unusual power of endurance enables him to live in the lumbering camps under poor, often intolerable hygienic conditions, and put in a winter's work in the deep snow at temperatures ranging to $-50°$ F.

The total population of the county has slightly decreased in the last 10 years. This is due to the mechanization of the mines and the decline of the lumber industry. The communities and families of the county have been stabilized and are largely the same since the war-period, 1916. Besides Finns, the largest groups of foreign born are French Canadian, Swedish, English (Cornish), and Italian. There are two or three Asiatics and perhaps 50 Negroes.

Social condition: It has not been possible to collect all information on all cases, but we believe that the figures which we offer give an adequate picture of the situation.

We have studied the parental home of the patients as showing the conditions under which they usually have spent the greater part of their lives.

The known occupations of the heads of the family were 41 per cent miner-farmers and 38 per cent farmers. The balance were laborers with the exception of three in commercial pursuits and one clergyman.

"The Finn is not a miner by nature. He is a man of the soil. After working in the mines a few years—the average is from two to five—he uses his savings for the purchase of some land or for taking up a homestead (2)."

As soon as he has taken up a piece of land, he builds a tiny shack and clears an acre; from this humble beginning he works during all the time free from the mines, until he has developed a real farm with a modern dwelling.

Housing: We describe an average dwelling. It is of wood, two stories, and in good sanitary condition. It stands alone on a lot large enough to furnish garden space. It has running water, electric lights, no bathroom, and an outside toilet. There are four rooms on each floor. The parents have their own bedrooms, and the children make shift according to number. Finnish homes are immaculately clean. A lack of ventilation is noticeable in nearly all homes of the Upper Peninsula. Sealed windows and doors are a means of combating the cold climate.

The average farm house is equally good. It is large and well built, has a good water-supply, good drainage, and is extremely clean. There, too, ventilation is lacking.

Of the Finnish patients studied, 58 per cent came from such average homes, 14 per cent from homes below this average, and 10 per cent from homes above the average. Fifty-five per cent were from average families with an income sufficient to supply the necessities of life to a decent degree. Twenty-five per cent were below average, and dependent on relief; two per cent were above average, and able to live in undoubted comfort.

Every member of an average family is expected to work hard and to be willing to sacrifice comfort and pleasure in the interest of his family, which is large. More than one-half of the patients have come from families ranging from 7 to 12 children, the average being 7+.

Twenty-seven per cent of the patients were born in Finland and 73 per cent in the United States, but 57 per cent of the families continue to live in the Finnish tradition, using the Finnish language at home. Twenty-eight per cent have adopted American standards.

There is said to be less illiteracy in Finland than in any other country. In Marquette County Finnish children are sent to school and show an aptitude for learning.

Finns seem stolid and phlegmatic, but on close acquaintance one discovers that individuals exhibit a wide variation in character and conduct. Their perseverance is mistaken for stubbornness; their pride and independence is interpreted as a lack of coöperative spirit. Having a few inelastic concepts, they are suspicious of innovations, but readily accept new ideas when their worth is demonstrated.

Their unusual physical strength and rugged health is outstanding. It enables them to do very hard work (and they love to work), with the result that most older patients, heads of families and mothers, have continued at their task until their disease is too far advanced for treatment. This ruggedness too may be the very reason for their mistrust of modern medicine. Older Finns pay no heed to the dangers of contagion and have a fatalistic attitude toward disease and death. When sickness occurs old wives' remedies are used till the patient is prostrated; and then, if medical aid is sought, advice is often disregarded.

The popular practice among Finns of taking group steam-baths in crude, unventilated shacks, followed by cold dips or by running through snow drifts, is traditional. These baths are thought to be curative, as well as cleansing, and it is said that "if a steam-bath cannot cure an ailment, nothing can."

For the purpose of this paper I have studied only the cases admitted

to Morgan Heights Sanatorium during the time that I have had charge. There have been additional cases reported as tuberculosis by physicians of the county, and 131 deaths of nonsanatorium patients by tuberculosis (all forms) reported during these nine years; 43 of these 131 deaths were known to be among Finns. My figures are, therefore, inconclusive, but I believe that they furnish a fair index to the situation.

I will not trouble the reader with many statistics at this time, but will summarize my tables.

Marquette County has a population of 44,000; the 442 cases that I cite represent a total morbidity rate of 10 per 1,000. The Finnish population is 22 per cent of the total population, but their morbidity rate is 20.7 per 1,000. Other nationalities comprise 78 per cent of the population and have a morbidity rate of only 6.3 per 1,000. For the purpose of this paper I have divided the cases into those of Finns and those of all other nationalities combined.

Forty-four per cent of all women admitted to Morgan Heights Sanatorium and 43 per cent of all the men admitted were Finns.

The only striking difference in the ages of all those admitted was that 86 per cent of the Finnish women were less than 30 years old, while 73 per cent of the non-Finnish women were more than thirty. Of all women admitted 94 per cent were under forty.

Of all cases admitted, 50 per cent were far advanced, 30 per cent moderately advanced, and 20 per cent minimal. I have omitted from my tables cases that were admitted for observation and proved not to have tuberculosis. The number of Finnish women exceeded the men by 12 per cent in the far-advanced group, by 22 per cent in the moderately advanced group, and by 50 per cent in the minimal group; while the number of non-Finnish women was equal to the men in the far-advanced group, and exceeded the number of men by 28 per cent in both the moderately advanced and the minimal groups.

Fifty-three and one-half per cent of the Finnish cases were from families in which there had already been one or more cases of tuberculosis: seven of these apparently were "conjugal tuberculosis."

Finnish patients have had no predominating occupation: there are mostly housewives, students, farmers and miners, in the order given. Marquette County's most important industry is mining, and about 5,000 men have been employed at this work during the last 10 years, of which about 40 per cent were Finns. But only 27 per cent of all men, who have entered the Sanatorium, were miners.

I have not observed any difference in the type and course of the disease in Finns from that of the usual type and course of pulmonary tuberculosis. I recall but 4 cases, 2 per cent, of miliary tuberculosis. The "good chronic" is hardly ever found among Finns.

I am convinced that the younger Finnish patients, now that there is confidence in the possibilities of cure, are fully as coöperative as those of any other nationalities.

TABLE 1

Tuberculin testing in Marquette County

AGE-GROUPS	NUMBER TESTED	POSITIVE	NEGATIVE
Finns			
		per cent	
Up to 10 years, inclusive	708	137 (19.3)	571
11 to 15 years, inclusive	768	242 (31.5)	526
16 to 20 years, inclusive	369	132 (35.7)	237
21 years and over	66	50 (75.8)	16
Total Finns	1,911	561 (29.3)	1,350
Non-Finns			
Up to 10 years,inclusive	2,897	269 (9.3)	2,628
11 to 15 years, inclusive	2,475	444 (18.0)	2,031
16 to 20 years, inclusive	982	233 (23.7)	749
21 years and over	207	124 (60.0)	83
Total Non-Finns	6,561	1,070 (16.3)	5,491
Finns	1,911	561	1,350
Non-Finns	6,561	1,070	5,491
Total tested	8,472	1,631 (19.3)	6,841

Results of treatment: Forty-four per cent of the Finns and 56 per cent of the others showed good results. There was a slight difference in the two groups in the ratio of unimproved, but the ratio of deaths was 35 per cent for the Finns to 20 per cent for the others. The sanatorium death-rate as a whole and in Finns has followed the steadily decreasing tuberculosis death-rate in the county during the nine-year period.

Collapse therapy: At the beginning of the period studied (1926) there had been very little done in the way of health education in Marquette county. Tuberculosis was regarded as an invariably fatal disease, and

the treatment at that time in the Sanatorium was a very sketchy version of the hygienic-dietetic type. Collapse therapy was absolutely unknown. During the first two years 5 patients were persuaded to permit the use of artificial pneumothorax. The numbers have slowly increased until at the end of the nine-year period 75 per cent of all patients in the Sanatorium had had one or more forms of collapse therapy, besides a number of discharged patients(19) who were returning regularly for their refills: this in spite of the fact that the Sanatorium must admit patients in any stage.

During the nine-year period 112, or 25 per cent of all cases, were given some form of collapse therapy. It so happens that my table shows 25 per cent of the Finnish patients and 25 per cent of all other patients had collapse therapy. There were good results in 57 per cent of all cases, and the ratio of Finns to non-Finns was about even.

There was little variation in the physical condition of the Finnish and non-Finnish groups at the beginning of treatment. Finns accepted collapse measures as readily as others and it is not exceptional for them to make these treatments a condition of their entering the Sanatorium.

Tuberculin survey: From 1926 until 1931 only contacts from patients' families were tested. We then began a systematic testing of the children in public and parochial schools, including the Northern State Teachers College in Marquette. Written consent from the parents was required. There was an average of 60 per cent of consents. My impression is that there were fewer consents from Finnish parents. The intracutaneous test was used in all cases in a dose of 0.1 mgm. of O.T. A total of 8,472 tests were given. Twenty-nine per cent of the Finnish group reacted, while 16.3 per cent of the other nationalities reacted. The ratio in the age-groups is striking. The Finns were 2 to 1 up to 10 years; 5 to 3 between 11 and 15; 3 to 2 between 16 and 20; and 5 to 4 in those more than 20 years.

SUMMARY

1. The Finns are an aboriginal people in the sense that their language and characteristics have remained unchanged for many centuries and that their country has never been invaded and settled upon by alien people.

2. The native environment in Finland presents all the handicaps common to poor European peasants. A constant struggle with Nature

calls for an unusual degree of courage and physical strength. The immigrants who have settled in Marquette County are from an isolated northern region of their country. Isolation has, therefore, tended to prolong their primitive social attitudes.

3. In Finland public-health measures have been recently instituted to combat a tuberculosis morbidity that is still the highest in Europe, although the death rate from nontuberculous diseases is comparable to that of the United States. The large part of the emigration occurred before this work had been started.

4. Those who have come to the Upper Peninsula continue life under the same type of climatic difficulties and react to the economic opportunities by undertaking extremely hard and constant labor.

5. In Marquette County the housing conditions are good, but large families create overcrowding and there is a general apathy toward proper ventilation.

6. Habits of perseverance and endurance, and an attitude of suspicion toward strangers and new ideas retard response to opportunities for early diagnosis and treatment.

7. Tuberculosis morbidity in relation to population is more than three times that of all other nationalities combined.

8. The proportion of far-advanced cases is higher. There seems to be no difference in the type of cases treated and in the course of the disease. The ratio of Finnish women to men in the ages below thirty was higher than in the other group. The results of treatment are less satisfactory and the number of deaths higher.

9. Response to collapse therapy equals the response shown by patients of other nationalities.

10. Finnish children have shown almost double the number of reactors found in the non-Finnish group.

CONCLUSIONS

My experience leads me to believe that the tuberculosis situation in Finnish colonies offers a direct challenge to the antituberculosis movement. Nowhere does one observe more plainly the value of the lessons of sanitation and hygiene given in the schools. This work must be continued and strengthened. Properly organized propaganda for early diagnosis, and prompt treatment must not be halted. Probably the most hopeful chance of success lies in easy access to medical advice, careful diagnosis and attractive sanatorium facilities, offering every opportunity

for treatment. In a word, the most potent argument for modern treatment is the patient who is discharged in good condition.

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TUBERCULOSIS MORTALITY AS AN INDEX OF HYGIENIC CONTROL[1]

Biometric Contributions to the Epidemiology of Tuberculosis

GEORG WOLFF[2]

1. INTRODUCTION

The epidemiology of tuberculosis has a leading place among the social biological happenings of the present time. From the beginning of the decline in tuberculosis mortality in most civilized states medical statisticians have given special attention to this phenomenon. It is not surprising that clinicians have seen in it primarily a result of their activities while economists and statisticians have devoted attention to a series of other factors falling within the field of modern industrial development and the science of population (1).

Coincidently with the decline of tuberculosis there has been an increase in the mortality from cancer, a new phenomenon of social pathology that has attracted general attention. Superficially, it might seem that there was some intimate biological connection between the increase of cancer and the decrease of tuberculosis. As we could show elsewhere, there is much reason to suppose that the apparent increase of the Cancer menace is but an appearance dependent upon changes in the age-composition of civilized races. In other words, not purely biological but rather sociological or social-biological factors are involved (2).

A further phenomenon accessible to biometric study is the physical growth of civilized people. Apparently, without direct connection with the social-biological and epidemiological happenings of the present day it is nevertheless referable to similar causes. I have had the opportunity of making systematic measurements and weighings in nine successive school years in Berlin since the Great War; and they demonstrated a real increase in the rate of growth (3). Over the period during which tuber-

[1] For the translation of this manuscript the author is very much indebted to Professor Major Greenwood, F.R.S. (London), who suggested to him the idea of giving a lecture on this subject in the London School of Hygiene and Tropical Medicine in the Spring of 1935.

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culosis declined, increased and then declined again, the growth-curves have shown changes in the opposite sense. Here also parallelism would suggest some common factor which would hardly be a direct biological effect but rather a general sociological-biological tendency which is of fundamental importance in determining general health conditions.

This tendency can be sought in the amelioration of existence of large masses of people and the raising of the standard of life in the course of the industrial development of most civilized states. After the control of initial difficulties this development has resulted almost everywhere in an *increase in power of consumption* but has been associated with *changes in the population structure* due to the declining birth-rate and increasing expectation of life. These changes are again associated with the general fall of infant mortality, of acute epidemic diseases, rickets, hereditary syphilis and tuberculosis, together with an increase of the rate of body growth, and increase in mortality from cancer (behind which a great increase in the expectation of life is hidden). I propose, with the help of biometric methods and population statistics, to discuss some of these questions, mainly basing myself on my own researches. And, in conclusion, I shall attempt briefly to state my position with respect to the fundamental question which at present so greatly interests students of comparative human biology and anthropology, namely: Can we from the appearances of human civilization of our day infer a biometric degeneration?—perhaps the verdict must be not proved. But never in scientific discussion should *a priori* philosophy take the place of objective measurement, or, in the stricter terms of the theory of knowledge, be independent of such experience; where numbers can rule they should rule (Pythagoras). To faith and true religion, needs of all mankind, this admission will never do wrong.

2. TUBERCULOSIS MORTALITY IN INDUSTRIAL AND AGRARIAN STATES

The rate of mortality from tuberculosis is still the best index of the hygienic culture of a population, and, as numerous researches have proved, is intimately connected with well-being and social status, even if a simple mathematical measure of this relation cannot be given (4). From the biopathological point of view tuberculosis is of course an infectious disease, but in its development is influenced by the bodily qualities of the individual and his inherited constitution. This, from the point of view of the practitioner, is of less importance since inherited constitution cannot be altered in later life.

Numerous attempts have been made by methods of immunology to increase bodily resistance to tuberculosis but without much success. It would indeed be a piece of biological magic if through some artificial immunization we could do better than the natural process of saturation which all inhabitants in our thickly populated civilized countries must pass through. The chronic course of tuberculosis suggests to the physician who thinks biologically that the methods of protective vaccination, which in some acute infectious diseases are reasonable, cannot be transferred to tuberculosis; for this disease, or passing through an attack of it, confers spontaneously no immunity against later attacks. Hence the success of such artificial methods has so far not been considerable. Consequently, social prophylaxis of tuberculosis takes the front of the stage, in a prophylactic handling of this disease of the people which claims so many of its victims from working ages of life; social prophylaxis will be helped in increasing measure by modern clinical or therapeutic measures directed to the service of the individual.

With these observations I pass directly to the theme.

In many circles it is almost a dogma that the increasing industrialization of a country is associated with an increase of tuberculosis. This is not tested but asserted. It would be interesting to study the development of rates of mortality from tuberculosis and industrialization in all countries over the last 50 years by means of international statistics (4). Unfortunately, comparable data are scanty and the task is difficult. For international comparisons are beset with numerous sources of error, such, for instance, as variations in medical facilities, varying frequency of autopsies and methods of certification. I have attempted to make some comparisons of mortality and industrialization in Europe, using the statistical measure of correlation but some precautions are necessary.

Mortality figures for tuberculosis do not necessarily reveal the true distribution of the disease, but must be used as the best available measure of comparison and as certainly superior to estimates of morbidity. The data of different countries are so much the more trustworthy in so far as the diagnosis on a death-certificate is the basis of the national statistics, and are consequently most to be relied upon in a country where medical inspection at death is obligatory. Apart from difficulties in the original material, which cannot be corrected by any arithmetical process, the method of statistical elaboration is of importance. In particular, variations in age-composition between town and country in different popula-

tions and in different occupational groups must be allowed for. This error is however of less importance in tuberculosis than in cancer owing to the former's relatively wide distribution in the age classes.

A measure of industrialization is best obtained by a census of occupations, which is, however, only made at long intervals: for instance, before the War, in the German Reich, 1907, Netherlands, 1909, Belgium, Switzerland and Austria 1910, France, Great Britain and Italy, 1911, and, after the War in most countries between 1920 and 1925. These censuses showed the percentages of occupied males in groups of occupations, among which the three groups, agriculture and forestry, industrial and mining, commerce and transport are much the largest. We thus obtain a picture of the extent to which industrial or agricultural activities are predominant in the population. Of course, in view of the development of industries no rigid schematization is practicable.

There are no such things as purely industrial or purely agrarian states; nevertheless, contrasts did clearly emerge from the official data of occupational censuses, as, for example, when we find that in Hungary, according to the census of 1910, of every 100 occupied persons 64.1 are engaged in agriculture and forestry and only 23.3 in industry and mining, trade and transport together; while in England and Wales in 1911 the corresponding figures are 8.5 and 72.8. In the post-War period the change has been comparatively small, for in Hungary at the census of 1920, 58.3 per cent were still engaged in agricultural pursuits and only 28.0 in industrial work, while for England the figures were 7.5 and 73.2. It is then permissible to speak of the agricultural type of state and of the industrial type of state. In the following summaries (table 1) countries are ranged in order of the proportion of persons engaged in industry and mining, trade and transport, as shown by the last census before and after the War. This proportion I have used as an *index* of industrialization to be correlated with the mortality rate from tuberculosis.

The last column of table 1 shows the rate of mortality from tuberculosis per 10,000 persons, in the last pre-War quinquennium 1906–1910, and similarly in table 2 the post-War quinquennium 1921–1925 so far as the figures are available. For obvious reasons the years immediately during and after the War are neglected. The period from 1906–1910 corresponds approximately to the epoch of the last pre-War occupational census; the period from 1921–1925 was one during which years most countries carried out an occupational census. A quinquennial group has been chosen to diminish the fluctuations attributable to the factor of

chance but of course the various material sources of error of international comparisons cannot be removed. What are we to learn from this comparison? The lowest rates of mortality from tuberculosis in the pre-War quinquennium are in the industrial states of Belgium and England. These follow in order, with also favorable figures, namely, less than 20

TABLE 1

Industrialization of European countries and mortality from tuberculosis before the War

COUNTRIES IN ORDER OF HIGHEST INDUSTRIALIZATION (COLUMN 5)	CENSUS YEAR	OF EVERY HUNDRED EMPLOYED THERE WERE ENUMERATED IN				DEATH-RATE PER 10,000 PERSONS LIVING FOR THE AVERAGE OF THE YEARS 1906–10
		Industry and Mining	Trade and Communications (including hotel services, etc.)	Both Groups	Agriculture and Forestry	
1	2	3	4	5	6	7
England and Wales	1911	46.9	25.9	72.8	8.5	15.68
Scotland	1911	49.4	22.8	72.2	11.8	20.21
Belgium	1910	50.7	17.4	68.1	16.6	12.88
Switzerland	1910	46.1	15.6	61.7	26.8	24.68
The Netherlands	1909	34.6	18.2	52.8	28.3	16.56
Germany	1907	40.0	12.4	52.4	35.2	17.53
France	1911	35.8	9.8	45.6	40.7	22.13
Norway	1910	26.3	15.1	41.4	39.2	24.00
Denmark	1911	24.9	14.9	39.8	42.7	16.24
Sweden	1910	25.7	10.5	36.2	46.2	?
Italy	1911	27.5	8.1	35.6	55.5	16.73
Austria	1910	24.3	8.8	33.1	56.9	30.53
Ireland	1911	21.9	10.8	32.7	43.0	25.26
Russia	1897	17.9	7.1	25.0	58.3	?
Hungary	1910	16.3	7.0	23.3	64.1	37.44
Spain	1910	14.6	5.4	20.0	56.2	17.62
Finland	1910	11.0	4.4	15.4	71.5	27.21 (only tuberculosis of lungs)

	Industrially Employed per cent (column 5)	*Mortality rate from tuberculosis per 10,000 (column 7)*
Mean	46.21	21.93
Standard Deviation	17.3	6.5
Coefficient of Correlation	$r = -0.647 \pm 0.105$	

deaths per 10,000: Denmark, the Netherlands, Italy, the German Reich and Spain. Then, with from 20–25 deaths per 10,000: Scotland, France, Norway and also Switzerland, while Ireland, Finland, Austria and Hungary in part have much higher rates. The latter are all, as a glance at the table shows, distinctly agrarian countries. Owing to a lack of official statistics, information regarding Russia and the Balkan States, where

mortality from tuberculosis, according to special investigations of particular towns, was high, cannot be provided for this period.

When a correlation coefficient between the industrial index and mortality from tuberculosis is calculated, as Prof. Greenwood and I have

TABLE 2

Industrialization of European countries and mortality from tuberculosis after the War

COUNTRIES IN ORDER OF HIGHEST INDUSTRIALIZATION (COLUMN 5)	CENSUS YEAR	OF EVERY HUNDRED EMPLOYED THERE WERE ENUMERATED IN				DEATH-RATE PER 10,000 PERSONS LIVING FOR THE AVERAGE OF THE YEARS 1921–25
		Industry and Mining	Trade and Communications (including hotel services, etc.)	Both Groups	Agriculture and Forestry	
1	2	3	4	5	6	7
Scotland	1921	54.3	20.7	75.0	10.1	11.6
England	1921	50.8	22.4	73.2	7.5	10.8
Belgium	1920	46.5	18.4	64.9	19.3	10.6
Switzerland	1920	44.3	16.6	60.9	26.0	15.5
The Netherlands	1920	38.0	21.3	59.3	23.6	10.9
Germany	1925	41.4	16.5	57.9	30.5	13.1
Norway	1920	29.4	19.7	49.1	36.8	19.5
Austria	1923	33.2	15.4	48.6	39.9	18.7 (1)
Czechoslovakia	1921	36.8	10.1	46.9	40.3	19.5
France	1921	32.1	14.2	46.3	41.6	19.4 (2)
Sweden	1920	31.1	14.3	45.4	40.7	14.8
Denmark	1921	27.3	16.8	44.1	35.2	9.3
Italy	1921	24.7	10.3	35.0	55.7	14.1
Irish Free State	1926	15.2	15.2	30.4	52.0	15.2
Spain	1920	23.9	5.4	29.3	57.0	15.4
Hungary	1920	18.5	9.5	28.0	58.3	29.3
Esthonia	1922	13.7	6.0	19.7	65.8	24.0
Finland	1920	13.1	6.1	19.2	70.4	23.8 (3)
Lithuania	1923	6.1	3.3	9.4	79.4	15.6

(1) 1923–1925; (2) only 1921; (3) only pulmonary tuberculosis.

	Industrially Employed per cent (column 5)	*Mortality rate from tuberculosis per 10,000 (column 7)*
Mean	44.35	16.19
Standard deviation	18.0	5.1
Coefficient of correlation	$r = -0.766 \pm 0.095$	

shown (3), we obtain the value of $r = -0.65$, that is to say, a high value, the negative sign of which shows that the indices vary in opposite directions. Behind this arithmetical index must naturally be hidden a whole series of factors. The standard of living, level of hygienic instruction, school instruction, social insurance, protection of workers and also,

acting in the opposite way, injuries due to factory labor, smoke, dust, alcoholism and so on.

In this period there was a great technical industrial development in all lands and plainly we have no room for any rigid explanation even if a tendency is unmistakable. There are, indeed, striking exceptions. Thus in Denmark and the Netherlands, mortality from tuberculosis was already very low before the War, possibly because their populations combined with a high average standard of living a high measure of physical and mental cultivation. On the other hand, tuberculosis mortality in Switzerland is high in spite of the fact that this state, according to the occupational census, must be reckoned as industrial. Sanatoria in the Swiss mountains are world famous; but, no doubt, the standard of living of the Swiss laboring classes is not very high and not comparable with that of wealthy sanatorium patients. The same remark applies to the Bavarian and Austrian highlands. But in all three populations which by customary standards live healthily the tuberculosis mortality figure is high. An exception on the other side is afforded by the pre-War figures for Italy with a relatively low mortality figure from tuberculosis in a predominantly agrarian population. The softness of the southern climate cannot be a sufficient explanation because in Northern Denmark an even more favorable tuberculosis figure is found.

When we think of all the factors which affect the problem of tuberculosis, environment, race, social status, climate, effect of the sun and so on, it is clear that we cannot reduce the problem to a simple effect upon the specific organism. I have discussed all these matters in greater detail in my monograph and some supplements, where the associations of the problem to industrial development in different countries in the pre-War period are set out (4) (5) (6). Instructive are, for example, the finer differences which can be made out from the official statistics of the three constituents of Great Britain. Far the most favorable for the quinquennium, 1906–1910, are the tuberculosis figures in highly industrialized England and Wales (15.7 deaths per 10,000), less favorable is the position of Scotland (20.2 deaths per 10,000), and far the worst Ireland (25.3 per 10,000) the population of which is in a great proportion agricultural. These differences are particularly striking, as here differences of climate could hardly play a predominant part. I would also allude to the striking differences in the tuberculosis mortality of the constituent states of the German Reich. For instance, highly industrialized Saxony had a lower figure (15.5 deaths per 10,000) than agrarian

Bavaria (24.5 per 10,000). Very similar results have been reached in a special investigation by F. A. Weber for Saxony (7), Berghaus for Baden (8), recently Scheel in Norway (9), Backmann and Savonen in Finland (10). It appears that in the industrial areas where the population lives under the most favorable economic, hygienic and cultural conditions, mortality from tuberculosis is at its lowest.

And how is the position since the War? Table 2 gives a general view. The pre-War correlation between industrial index and tuberculosis mortality in 14 countries in 1906–1910 was $r = -0.65$ (table 2). With 19 countries in which measurements for 1921–1925 were available r was -0.77. If anything, then the relation has become sharper. Let us again examine the individual figures ranged in order of industrialization: Scotland and England, and Belgium are at the top; in agreement with pre-War experience they have a low rate of mortality although the agrarian state of Denmark has an even lower rate. In Denmark, the position is at its most favorable. In general, however, the typical agrarian states, Hungary, Esthonia and Finland have still the highest figures of mortality from tuberculosis. In Lithuania recorded figures are certainly less than the real figures. Here the statistics of causes of death are little cultivated. The mean figures for Norway, Austria and Czechoslovakia are also high.

So there has been little change in the general tendency since the War, although the average level of tuberculosis has fallen appreciably. It is worthy of note that Italy has rather lost her favorable position; although with a rate of 14.1 per 10,000 she is still much below the mean for all countries, she has lost her superiority over Germany, which in 1921–1925 had a rate of mortality of only 13.1 per 10,000. Here, the influence of industrialization has shown itself in a typical way. Certainly the type of climate of Italy and Germany is not likely to have changed, nor biological susceptibility to tuberculosis, nor the natural constitution of the population; other factors must be invoked. These may perhaps be sought in a change in the social economic and social biological structure of the two lands. I do not propose to enter here into a further analysis.

Nobody who has any familiarity with industrial development during recent decennia will of course be content with such a facile explanation of the relation between mortality from tuberculosis and industrialization as that factory labor is in itself healthier than agricultural labor or that the inhalation of smoke and dust is a factor inhibitory to the development of tuberculosis. But it is not unreasonable to urge that the standard of

living associated with industrialization, the increase in the general level of culture produced by a compulsory education, improvement in the measures of protection for workers and the carrying out of numerous hygienic reforms, have indeed overcompensated the earlier injuries which

TABLE 3

*Secular trend of mortality from tuberculosis in Europe 1871–1900. Rates per 10,000 of the mean population**

COUNTRIES PLACED IN ORDER OF THE RATE OF MORTALITY IN 1926–30	1871–1875	1876–1880	1881–1885	1886–1890	1891–1895	1896–1900
1. Denmark (1)	—	31.3	30.5	28.9	26.9	21.6
2. The Netherlands	—	—	—	—	—	—
3. Germany	—	—	—	—	—	—
4. Prussia	—	31.7	31.3	29.0	24.7	20.8
5. England and Wales	29.4	28.9	25.4	23.2	21.2	19.0
6. Scotland	35.6	33.6	29.7	25.8	24.1	23.4
7. Belgium	33.6	32.3	30.1	—	28.8	24.9
8. Italy	—	—	—	20.8	19.2	18.1
9. Sweden (2)	—	—	—	—	—	—
10. Ireland (3)	25.3	26.6	26.6	26.9	27.5	28.3
11. Switzerland	—	—	27.1	27.0	25.4	24.6
12. Spain	—	—	—	—	—	—
13. Norway	—	—	—	—	—	26.9
14. Austria	—	37.7	39.3	38.3	39.4	34.0
15. France	—	—	—	—	—	—
do. (only towns) (4)	—	—	—	—	33.6	32.4
16. Hungary	—	—	—	—	—	32.8
17. Finland (5)	41.4	36.7	25.5	25.6	—	27.3

* Statistical data down to 1910 are taken from *Statistique internationale du mouvement de la population* (*Statistique générale de la France, Paris 1907 and 1913*); subsequently from the year-books of the International Statistical Institute (The Hague) and the monthly report of the Section of Hygiene of the League of Nations (Geneva), particularly from a report on mortality from tuberculosis of 15th February and 15th March, 1931, (*tenth year nos. 2 and 3*), supplemented by data contained in the *Internationalen Uebersichten der statistischen Jahrbücher für das Deutsche Reich, 1928–33.*

(1) Down to 1914 only for urban areas, since 1920 for the whole country.

(2) Down to 1910 only a few towns reported on pulmonary tuberculosis. Since then all forms of tuberculosis for the whole country. The earlier figures are accordingly not comparable with the later ones.

(3) Since 1919 only for the Irish Free State. (4) Towns with more than 5,000 inhabitants.

(5) Only pulmonary tuberculosis; since 1926–30, all forms of tuberculosis.

factory labor did to public health (as for instance, in England in the pre-1832 period of monstrously excessive child labor). A diminution of mortality from tuberculosis is not peculiar to either industrial or agricultural states. All that is contended is that in an agrarian state the technical hygienic and educational developments which are the condi-

tions of diminishing tuberculosis mortality develop more slowly than in an industrial state. Evidence of this is afforded by a *chronological comparison* of tuberculosis mortality for European countries to which I now turn.

Tables 3 and 4 provide some particulars respecting European states so far as data were available. It must not be forgotten that there have been in some instances important changes in boundary during the last fifty years and that new states have been created. In many of the newly

TABLE 4

Secular trend of mortality from tuberculosis in Europe, 1901–1930. Rates per 10,000 of the mean population

COUNTRIES PLACED IN ORDER OF THE RATE OF MORTALITY IN 1926–1930	1901–05	1906–10	1911–15	1916–20	1921–25	1926–30	1876–1880 (MEAN IN LATER PERIOD) = 100
1. Denmark (1)	19.3	16.2	14.2	14.2	9.4	7.6	24
2. The Netherlands	18.7	16.6	14.6	17.5	10.9	8.7	(47)
3. Germany	20.7	17.5	15.0	19.3	13.2	8.9	(43)
4. Prussia	19.1	16.2	14.3	19.0	13.2	9.1	29
5. England and Wales	17.4	15.7	14.1	15.4	10.8	9.4	33
6. Scotland	21.6	20.2	16.9	14.7	11.6	9.5	28
7. Belgium	—	12.9	12.4	17.3	10.6	9.5	29
8. Italy	16.7	16.7	15.5	17.7	14.2	12.7	(61)
9. Sweden (2)	—	—	19.3	18.0	14.8	13.1	—
10. Ireland (3)	27.6	25.3	21.5	20.2	15.2	13.8	52
11. Switzerland	26.5	24.7	19.9	19.3	15.5	13.9	(51)
12. Spain	19.9	17.6	15.4	18.0	15.4	14.0	(70)
13. Norway	25.6	24.0	21.9	20.5	19.5	15.5	(61)
14. Austria	34.1	30.5	28.3	40.7(6)	21.2	15.8	42
15. France (4)	—	22.1	21.0	22.7	20.5(7)	16.6	—
16. Hungary	39.6	37.4	32.9	33.0	29.3	22.5	(70)
17. Finland (5)	29.1	27.2	25.5		23.8	24.1	66

(1–5) As in table 3; (6) 1916–1918; (7) only 1921 and 1925.

created states comparable data in the period before the war are not obtainable. Also the German Reich has suffered a considerable loss of territory. Apart from this, the registration of causes of death for the whole of the German Reich does not extend far back in time, and consequently in the table I have substituted Prussia, the certification of statistics of which go much farther back. Much the greatest decline is in the following countries, put in order: Denmark, Scotland, Belgium, Prussia, England and Wales. All except Denmark are highly industrialized states. Even in Austria there is a considerable reduction, par-

ticularly after the War, if we begin with the hereditary lands, which is perhaps not entirely without objection. The diminution is much less in Switzerland, Ireland and Finland, also in Norway, Italy, Spain and Hungary, where, however, the points of departure of the statistics in time do not extend equally far back. Hungary and Finland had still in the quinquennium 1926–1930 uncommonly high mortality figures and in other countries the data cannot be followed sufficiently far back. This is true for the whole of Sweden, although in particular towns and for pulmonary tuberculosis, Sundbärgs's famous calculations are based upon data going very far back. France again, whose mortality figures for the whole country also do not extend far back in time,—somewhat further for towns with more than 5000 inhabitants—still exhibits high rates of mortality; in the period before the War there was no sign of a diminution.

Various results are most clearly seen if we measure the fall of tuberculosis by means of some index number (see last column of the table 4). To this end we take the mortality rates of the quinquennium, 1876–1880, and express our rates in these terms: in those countries in which during that period there were no figures for these specific rates of mortality and consequently no rate of mortality from tuberculosis obtainable, the comparative figure is based upon a later year. It will be seen that in the above cited industrialized countries and in Denmark tuberculosis mortality has fallen to less than a third; in Denmark, actually to a quarter of the chosen standard. In Italy and Finland the figure is still in 1926–1930 two-thirds of the initial figure; in Hungary as much as seven-tenths of the rate in 1896–1900; in the pre-War period there even seems to be a suggestion of increase in Hungary. Also in Ireland, Switzerland, Spain and Norway the pre-War diminution of mortality from tuberculosis was extremely modest. In these countries after the War an appreciable diminution has taken place.

I have limited myself to the *European* countries but trust that similar comparisons will be made in other Continents. I permit myself only to give a pair of indices from the U. S. A. and Japan. In the United States the tuberculosis mortality has fallen as industrialization has increased. The registration states, which are unequal in size, show that the rate of mortality from tuberculosis during 1906–1910 was 17.3 per 10,000; in 1921–1925, 9.3; and in 1926–1930, 7.9. The mortality figure is accordingly in these states as favorable as in part of Europe, whereas in the young industrial state of Japan mortality from tuberculosis is still high

and there is little indication of an improvement. The rate of mortality in Japan during 1906–1910 is 20.2 per 10,000; in 1921–1925, 20.3; in 1926–1930 still 19.1. Only in very recent years has a slight improvement become manifest. However, details will be found in Prinzing (11), Roesle (12) and Frederick L. Hoffman's report (13) and in the monthly epidemiological reports of the Section of Hygiene of the Society of Nations, especially of 1931 (14).

The secular evolution in all these countries is unequivocally in favor of the industrialized states, and accords with the general principles laid down by Newsholme (15) together with those emphasized by Teleky (16) and Rosenfeld (17) for the industrial areas of Austria. There is no contradiction between this result and the fact that within the same states mortality in agricultural districts or in agricultural occupations is frequently lower than in urban districts or industrial occupations. When the general conditions of life are approximately equal, those engaged in agricultural occupations will always enjoy the advantage of being engaged in the open air and it is when one compares the different countries that the influence of general culture and standard of living becomes striking. In industralized countries the agricultural laborer partakes of the successes of modern technical improvements in hygiene; he lives in England, Saxony or Denmark under very different conditions from those of Hungary, Finland or Russia. Thus can be explained the superficial contradiction between individual clinical experience and results of statistics, which, after all, merely express the sum of this experience freed from mere chance fluctuations.

Recently some writers have put the theory of selection in the foreground, a doctrine long ago used by Karl Pearson (18) to explain the decline in mortality from tuberculosis. Natural selection due to early death cannot sufficiently explain the epidemic course of tuberculosis in the industrial and the agricultural states because the power of reproduction of the tuberculous is in so many cases continued almost to death; so that a handing on of the tuberculous inheritance would be assured if heredity alone is the determined factor. This hypothesis of a natural elimination contrasts strongly with the view of other students of inheritance, who have seen in the previous decline of tuberculosis an undesirable increase of latent hereditary quotas, and logically demand the sterilization of all victims of open tuberculosis before the age of reproduction. This is at least logical even if based upon a self-contradictory hypothesis. For the here-proclaimed negative selection of modern hygiene and social

politics (so often asserted by social Darwinians and racial hygienists) seems to be in contradiction to the *facts* of epidemiology and improvement in expectation of life. Indeed, since the time of Robert Koch this plan of combating tuberculosis seems to have lost its meaning.

3. SUMMARY AND CONCLUSIONS

Here I conclude my brief account of the epidemiology of tuberculosis before and after the War. The increasing industrialization of civilized nations brings with it not only industrial diseases and accidents but also economic improvement of the mass of a population and, not less important, general enlightenment respecting cultural and hygienic questions. These advantages of industrialization and many other factors are influenced by the standard of living and legal measures for the protection of the worker, and for his education, so that the undoubted evils of industrial work are more than compensated. Compulsory education and social hygienic measures claim the foremost place. In consequence there can be no surprise that, on the whole, mortality from tuberculosis has improved more in the industrial than in agrarian states; is lower in the industrial areas of Germany and in England than in the Alpine lands of Austria, Bavaria and Switzerland or on the Steppes of Russia and the Plains of Hungary. A summary expression of this relation is given by the high negative correlation between Tuberculosis mortality and industrial indices.

The further campaign against tuberculosis, which should sometimes be regarded as a disease of ignorance, sometimes of bad housing, sometimes as a pure infectious disease, sometimes even as an inherited evil, is to be followed along the path of social biological and social hygienic development in civilized countries. Clinical and therapeutic methods, the improvement of which in our own time deserves our highest admiration and which it must always be the duty of the physician to employ, will aid the collective task of society. The general course of tuberculosis-epidemiology in the next years will, as our experience in the World War demonstrates, in the first place depend upon the *nutrition of the bulk of the people.* It is a singular conclusion of social economic development that in agrarian countries, the fundamental sources of production of food, national nutrition is on the average worse than in industrial countries. These inferences from demographic data—which should correct some popular dogmas—do not in any way affect the statement that agricultural production is vital to a growing industrial society. As I wrote in 1925,

at the end of my monograph on "The Mortality from Tuberculosis in Europe," agriculture is, and this is a truism, of fundamental importance for the preservation of the country and society; cultural hygiene, however, leaves too much to be criticized, particularly in purely agricultural states in which the results of modern technical improvements have not yet been implemented. In the industrial countries and in those with the mixed type of organization which carry with them the best guarantee of their existence, both agricultural economy and hygiene have improved under the influence of technical advance. This is demonstrated by, among others, the figures of tuberculosis mortality as indices of hygienic culture.

Are we entitled on the basis of these data (and many other) to speak of the biological degeneration associated with hygienic culture as some social Darwinians and racial hygienists tend to do? Are the inferences from the statistics of increased length of life, of increased bodily growth of school-children and recruits, from facts of epidemiology, social pathology and anthropometry to be so completely ignored, or do the critics not know these conclusions? For, in truth, figures speak a totally different language from that of the hypothesis of degeneration. According to them, man in the course of historical culture has not degenerated, at any rate has not become weaker and smaller; on the contrary, he offers resistance against illness and lives longer, so far as exact measurements can give information. This information relates indeed only to the *phenotype* which alone is accessible to our senses; beyond this, even the glorification of hereditary value and the biological selection of the superman, is metaphysics and metabiology.

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CHANGES IN PULMONARY TUBERCULOSIS FOLLOWING HAEMOPTYSIS

Clinical and Morphological Types and Their Evolution[1]

DAVID REISNER

Although haemoptysis has always occupied a leading position in the symptomatology of pulmonary tuberculosis, comparatively little attention seems to have been paid to its sequelae and its effect on the evolution of the disease. Apart from a cursory mention of the fact that a profuse haemorrhage may occasionally be the direct cause of death, or that it may result in an acute aggravation of the pulmonary lesion, one finds but little reference to the question of posthaemoptysis pulmonary complications.

Acute and alarming complications resulting from haemoptysis are not frequently met with in pulmonary tuberculosis. It is a well-known fact that a haemorrhage resulting in sudden death, either from suffocation caused by massive aspiration or from an extreme loss of blood, is an infrequent occurrence in pulmonary tuberculosis. Another acute, though not fatal, complication caused by haemoptysis, to which attention has been drawn in recent years, is the massive collapse of the lung resulting from a sudden occlusion of a large bronchus by a blood-clot. Such instances have been reported by Jacobaeus and Westermark (1), Wilson (2), Kylin (3), Saye (4), Rosenblatt (5) and Stivelman (6). However, this complication is likewise a rather rare occurrence in comparison with the frequency of haemoptysis in tuberculosis. Only few instances of massive collapse could be observed in a large material studied here.

It seems, therefore, that the real clinical significance of the complications following haemoptysis lies not so much in those acute but unusual events, as in the less dramatic and considerably more common sequelae and their influence on the course and prognosis of the tuberculous lesion. In this study an attempt has been made to define a group of clinically and morphologically characteristic types of pulmonary changes resulting from haemoptysis and, furthermore, by following the subse-

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quent evolution of these changes to determine to what extent they have a bearing on the progress of the disease.

The incidence of haemoptysis in pulmonary tuberculosis observed by various authors shows considerable variations. Schroeder (7) found 22.3 per cent, Sorgo (8) 38 per cent, and Norris and Landis (9) 47.6 per cent. In the material of the Tuberculosis Service of the Metropolitan Hospital, New York, which comprises upward of 5,000 patients, there was a record of frank haemoptysis on one or more occasions in 1,405 cases, or in 27 per cent. Findings suggesting that a spread of the pulmonary lesion had taken place as a result of the haemoptysis were present in 203 cases. However, only about one-half of this group could be considered as a suitable basis for detailed study. Only those cases were selected in which the sequence of events and the pulmonary findings were sufficiently definite to indicate a causative relation between the haemoptysis and the resulting changes in the lungs. It seems of particular value that in the predominant majority of these cases the subsequent evolution and the ultimate fate of the pulmonary lesion could be closely studied.

From the data just mentioned, the impression might be gained that posthaemoptysis changes in the lungs represent a relatively infrequent occurrence in comparison with the total incidence of haemoptysis in pulmonary tuberculosis. It is felt, however, that the above figures cannot be regarded as a true index and, therefore, do not permit an accurate statistical evaluation. It must be pointed out that most patients entered the institution after a considerable length of time had elapsed since the occurrence of the haemoptysis and, furthermore, that the majority of the cases presented advanced lesions at the time of admission. In such cases it is often extremely difficult to differentiate between changes due to spontaneous progression of the lesion and those which resulted from a spread following haemoptysis.

TYPES OF POSTHAEMOPTYSIS LESIONS

A division of the posthaemoptysis pulmonary complications into the following main types suggested itself in the course of this study:

1: Atelectasis, massive or lobar ..... { transient / permanent

2: Massive pneumonic lesions ..... { resolving / progressive

3: Diffuse focal disseminations ..... { resolving / stationary / progressive

The guiding principles for this subdivision were the morphological features of the changes in conjunction with the mode of their subsequent evolution, as revealed by clinical and roentgenological follow-up study. Although the writer is well aware of some distinct shortcomings in the above schematic grouping, it is offered here because it seemed to be the one least prejudicial. A division along aetiological lines, that is, a differentiation between changes of a specific and nonspecific character would, of course, be desirable. However, since it is extremely difficult in many instances to draw such a strict line of division, this is omitted from the headings, the differential points to be taken up separately with each of the following groups.

1. Atelectasis

Only cases showing the typical findings considered as characteristic for this condition were included here. In this series, there were found but few such instances. There were 6 cases with massive involvement of an entire lung and two in which the atelectasis was limited to one lobe. Cases of acute posthaemoptysis atelectasis, which are followed by complete restitution and a return of the lung to its original condition, seem to be quite rare. In all cases of this group the pulmonary changes were of a chronic and evidently permanent nature. In 2 cases of acute collapse, partial clearing with reaeration of the lung could be observed within a period of a few days; but, on further follow-up, there was evidence of progressive tuberculous changes which were obviously due to a spread of the lesion resulting from the haemoptysis.

The clinical and radiographic findings in cases of chronic massive atelectasis are essentially the same as the well-known findings observed in the acute form and a detailed description can therefore be omitted here. The posthaemoptysis forms of chronic atelectasis usually show evidence of an ulcerative and cavernous tuberculous process, associated with secondary bronchiectasis, in addition to the features indicative of atelectasis. The contralateral lung, as a rule, presents a marked degree of compensatory emphysema. Massive unilateral tuberculous lesions of this type, with signs of shrinkage of one side of the thorax and pronounced retraction of the mediastinal structures and heart, are often referred to as postpleuritic forms of pulmonary tuberculosis which is

meant to indicate that these changes are the result of a chronic obliterative pleuritis of long standing (Neumann (10)). In recent years, however, the occurrence of atelectasis in tuberculosis has been stressed by a number of observers. It is now well recognized that the underlying condition in a considerable proportion of such cases is a diffuse atelectatic shrinkage of the lung, probably not infrequently caused by a preceding haemoptysis. In a number of such instances, a free pleural space can be found when artificial pneumothorax is induced and the atelectatic lung can then be clearly demonstrated on the roentgenogram. An important indication of atelectasis is a high negative intrapleural pressure. On the other hand, it should be pointed out that in addition to the atelectasis, a coexisting obliterative pleuritis may be present in such instances. This is especially the case in the chronic forms in which the pulmonary lesion may give rise to chronic inflammatory changes of the pleura. The accompanying pleural changes, which result in fixation of the lung, account for the fact that definite respiratory pendulum movements of the mediastinum are only rarely observed in cases of massive chronic atelectasis complicating tuberculosis.

The question regarding the pathologicoanatomical changes in the chronic and permanent forms of posthaemoptoic atelectasis cannot be quite satisfactorily answered since postmortem studies on such cases are not available. It seems that this term defines a clinical rather than an anatomic entity. It is most probable that the underlying pathological changes are extensive fibrosis and induration of the lung with cirrhotic contraction, a condition known as collapse induration. It seems quite unlikely that such extensive changes of permanent nature could result from an occlusion of the bronchi caused by simple aspiration of blood following haemoptysis. The development of a chronic inflammatory process is probably an essential factor in bringing about lasting changes of such an extent. How much of this is due to the aspiration of tubercle bacilli and how much to coexisting nonspecific chronic pneumonic changes is, of course, impossible to determine. From the clinical standpoint it is especially noteworthy that such cases show little tendency to progression of the tuberculous process despite the permanently positive sputum. The contrast between the exceedingly chronic and stationary clinical course on the one hand, and the massive involvement of the lung on the other, are often very striking. This favorable course is in conformity with the recently advanced views on the rôle of atelectasis as a factor promoting healing in pulmonary tuberculosis. The

importance of the resulting change in the chemistry of the soil and its adverse effect on the growth of the tubercle bacilli were particularly emphasized by Coryllos (11). The clinical and experimental observations of Adams and Singer (12) point in the same direction.

The following two cases may serve as examples of massive atelectasis resulting from haemoptysis:

Case 4,286: G. H., male, aged 38 years, Negro, was admitted to the Tuberculosis Service of the Metropolitan Hospital on October 6, 1934. He had had symptoms of pulmonary tuberculosis since August, 1934. Roentgen examination showed an apparently recent cavity in the upper lobe of the left lung; the sputum was positive for tubercle bacilli. On September 12, 1934, pneumothorax had been instituted on the left side. On admission the patient appeared quite comfortable. He was practically symptom-free and the pneumothorax treatment was continued. A roentgenogram of November 7, 1934 (figure 1A) demonstrated a partial pneumothorax on the left side with very little collapse of the lung, the cavity in the upper lobe not influenced by the pneumothorax. On November 9, 1934, the patient had a profuse haemoptysis following which his temperature rose to 104°. He became considerably dyspnoeic and examination indicated a total collapse of the left lung. Roentgen examination on November 13, 1934 (figure 1B) demonstrated a complete collapse of the left lung; the cavity could not be seen. There were no symptoms or signs indicative of spontaneous pneumothorax. After a stormy course which lasted for about one week all the acute symptoms subsided. The pneumothorax treatment was continued. The lung remained completely atelectatic and the previously positive sputum became persistently negative, beginning March 15, 1935.

In this case the atelectasis which followed the haemoptysis most probably aided in bringing about the effective collapse of the lung. The disappearance of the cavity shortly after the occurrence of the haemoptysis is a noteworthy feature. The markedly toxic symptoms which followed the haemoptysis were in all probability due to a coexistent pneumonic infiltration. This may also explain the relatively large size of the collapsed lung, as shown on the roentgenogram.

Case 6,436: H. M., female, white, aged 17 years, was admitted to the Tuberculosis Service of the Metropolitan Hospital on March 24, 1933. She had had a pleural effusion on the left side four years prior to admission, and for one and one-half years had been under treatment for pulmonary tuberculosis. Roentgenogram of August 23, 1932 (figure 2A) showed a tuberculous lesion of chronic fibrocaseous character in the upper lobe of the left lung with a small

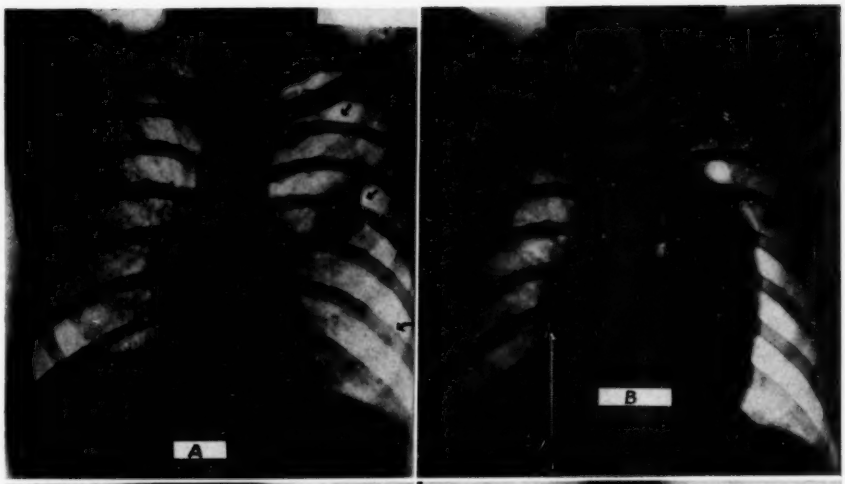

FIG. 1A FIG. 1B

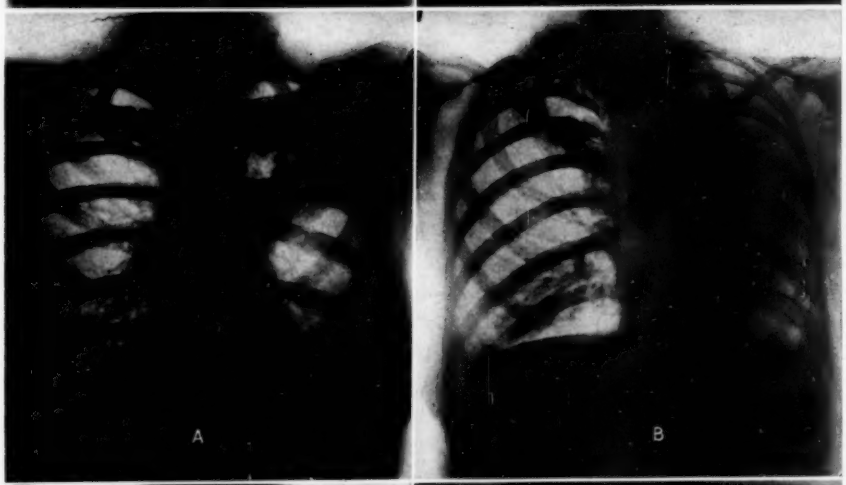

FIG. 2A FIG. 2B

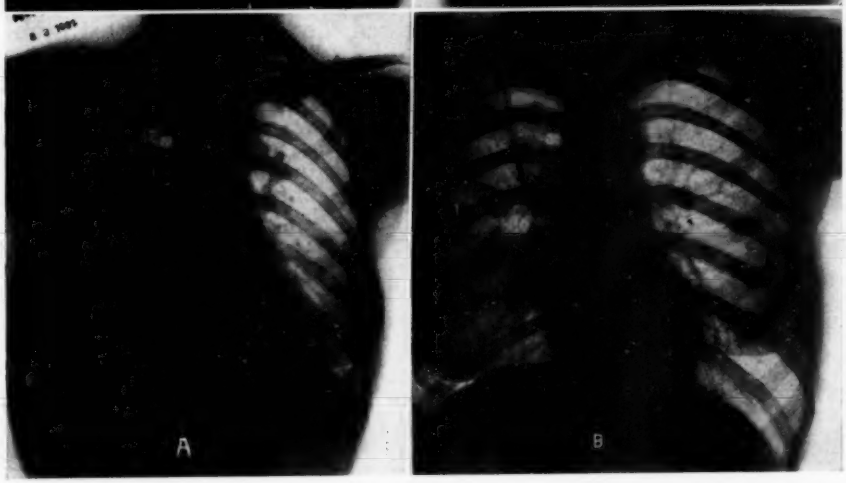

FIG. 3A FIG. 3B

cavitation in the infraclavicular area. The retraction of the mediastinum and heart to the left was probably due to the combined effect of the pulmonary lesion and of the residual pleural changes. Six weeks before admission, the patient had a profuse haemoptysis and brought up about three cups of blood. On admission she complained chiefly of pain on the left side of the chest; the temperature was normal with an occasional rise to 100°. Examination revealed marked dulness over the entire left side, altered breath-sounds and coarse râles over the upper lobe and absent breath-sounds from the 7th dorsal spine down. A roentgenogram of March 24, 1933 (figure 2B) showed atelectasis of the left lung, with marked retraction of the mediastinum and heart and elevation of the left diaphragm. Two small cavities were present in the upper lobe. The sputum contained numerous tubercle bacilli. On March 27, 1933, artificial pneumothorax was instituted; the intrapleural pres-

FIG. 1. Roentgenogram of November 7, 1934 (A) showed a partial pneumothorax on the left side (arrows). The lung was expanded and there was a cavity in the lower portion of the upper lobe. On November 13, 1934, four days after haemoptysis (B), there was complete collapse of the left lung; the cavity was not seen.

FIG. 2. Roentgenogram of August 23, 1932 (A) showed a tuberculous lesion of the fibrocaseous type in the left upper lobe with cavitation. There was thickening of the interlobar pleura and moderate retraction of the mediastinum and heart to the left. On March 24, 1933, six weeks after haemoptysis (B), there was massive atelectasis of the left lung. The heart and mediastinal shadow show a marked shift to the left, and the left side of the diaphragm is elevated. The right lung presents an emphysematous appearance.

FIG. 3. Roentgenogram of August 3, 1932 (A) showed an infiltrative process in the right upper lobe and a massive pneumonic involvement of the lower two-thirds of the right lung resulting from a recent haemoptysis. Roentgenogram of October 20, 1932 (B) revealed marked clearing of the pneumonic process. There can be seen a diffuse dissemination of small foci through the entire right lung.

sure was highly negative, −26 on inspiration. Roentgen examination after injection of 300 cc. of air revealed complete atelectasis of the left lung. The upper lobe appeared broadly adherent to the chest-wall. Because of failure to obtain a satisfactory collapse of the cavities, the pneumothorax treatment was discontinued and a total thoracoplasty was subsequently performed with apparently good results.

2. Massive Pneumonic Lesions

The cases included in this group presented pneumonic involvement of massive extent, developing as a result of haemoptysis. In a number of instances, the lesion occupied practically an entire lung; in others the involvement was lobar in character, and in still others the distribution was of the coalescent patchy type. In some cases of this group, the

lesion was limited to one side; in others, infiltrations of lesser extent could be seen in the contralateral lung, usually in the basal portions. Although it cannot be denied that atelectasis of varying degree probably plays a part in the production of such pulmonary changes resulting from aspiration, these cases were separated from the preceding group, as they failed to present the characteristic features of massive atelectasis. From the clinical standpoint, a clear distinction must be made between the transient forms of pneumonic infiltrations which undergo resolution and lesions in which the changes are of a permanent nature, and which represent an acute massive progression of the tuberculous process.

In the resolving forms the immediate reaction following the haemoptysis may be that of an acute respiratory affection with marked constitutional signs and symptoms, considerable elevation of the temperature and more or less marked dyspnoea. The examination of the chest rarely reveals characteristic signs of pneumonia. Usually there is found dulness on percussion and diminished intensity of breath-sounds. The most significant finding is the presence of diffuse moist râles, especially over the basal portion. The roentgenographic findings are, as a rule, much more pronounced than the physical signs, and reveal extensive pneumonic involvement of the types mentioned before. During the subsequent course, the acute manifestations subside quite rapidly, frequently within several days. Some of the abnormal physical signs may persist for a variable length of time, chiefly scattered râles over large pulmonic areas. The follow-up roentgen examinations reveal a variable behavior in the subsequent evolution of the lesions. In some instances, there may be noted a rapid and almost complete disappearance of the pneumonic infiltration within a period of several days. More frequent, however, is a slow and gradual resolution, the process of clearing extending over a period varying between a few weeks and several months. In a number of cases residual disseminated small foci persist for a long time, eventually undergoing resolution. In others, these foci become permanent and assume the character of discrete small nodules of the stationary type, as seen in the chronic disseminated productive forms of tuberculosis.

In contrast to the forms which show signs of resolution are those cases in which the posthaemoptysis complication results in a massive spread of the tuberculous lesion. The immediate clinical manifestations as well as the roentgen findings may be quite identical in both instances. The subsequent course, however, is decidedly different in the latter

group. In these cases the toxic symptoms do not subside; the elevation of the temperature and the other constitutional signs persist. The findings on physical examination become more pronounced, indicating a progressive and destructive type of involvement. The patients run a progressively downhill course and, as a rule, die within a period ranging between a few weeks and several months. Follow-up serial roentgen-ray studies reveal a rapid progression of the lesion in most instances. Definite cavity-formation within the massive pneumonic areas is not frequently observed. This is probably due to the rapidly fatal termination in the majority of such cases. In patients in whom the course was more chronic in character, progressive breaking-down of the massive lesion with excavation could be demonstrated. From the roentgen findings observed here the impression was gained that a predominantly unilateral massive tuberculous pneumonic lesion, extending down to the base, may be regarded as an indication of an acute posthaemoptysis spread.

As to the underlying morbid changes, a distinction must again be made between the progressive and the resolving forms of massive pneumonic lesions. In the former the anatomical findings are quite obvious. The most prominent features are extensive caseopneumonic changes, either massive, or lobar, or else consisting of numerous confluent lobular and acinous foci. The massive homogeneous opacity frequently found on the roentgenograms of such cases is due to the fact that surrounding the areas of caseopneumonic involvement there are almost invariably additional changes present, such as perifocal inflammation, oedema and zones of atelectasis. The contralateral lung often shows more or less widely scattered caseous foci, acinous or lobular in distribution. Evidence of well-defined cavitations within the fresh caseopneumonic areas may or may not be found, according to the duration of the spread.

In the benign forms the nature of the pathological changes is not clearly established. It is very probable that a combination of changes of heterogeneous origin is responsible for the clinical and radiographic findings in such cases, although it must be admitted that their exact differentiation is exceedingly difficult because of lack of postmortem studies in these instances. However, observation of the evolution of these lesions offers important clues. Thus, a rapid and complete resolution of the changes indicates an ordinary nonspecific aspiration pneumonia, possibly combined with some degree of atelectasis. On the other hand, those cases in which the process of resolution is incomplete

and slow, extending over a period of months, exhibit great similarities with the benign and evanescent exudative infiltrations of tuberculous origin. The persistent focal lesions frequently observed in such instances after absorption of the massive infiltration, strongly suggest that the aspiration and dissemination of tubercle bacilli play a part in the development of such posthaemoptysis changes.

The question arises whether there is any correlation between the subsequent evolution of the posthaemoptysis changes and the character of the preëxisting pulmonary lesion. It was observed that in those cases, in which the massive spread resulted in a rapid and fatal progression of the tuberculous process, the preëxisting pulmonary lesion almost always presented the clinical and radiographic features of the progressive and destructive, caseocavernous type of pulmonary tuberculosis. In the

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FIG. 4. Roentgenogram of May 13, 1935 (A), shortly after the occurrence of repeated haemoptyses, showed a large cavity in the right upper lobe and coalescent bronchopneumonic infiltration down to the base. On June 11, 1935 (B) there was evidence of extensive progression, with massive consolidation of the entire right lung and scattered foci on the left side.

FIG. 5. Roentgenogram of June 3, 1930 (A) showed an area of infiltration occupying the apex and subapical portions of the right upper lobe, the remaining lung fields were clear. On June 24, 1930 (B), about two weeks after several haemoptyses, there could be seen a diffuse dissemination of soft foci throughout both lungs, and on September 17, 1930 (C) there was extensive progression of the disseminated spread.

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resolving forms of massive posthaemoptysis infiltrations, on the other hand, the favorable evolution was not limited to these changes, but was equally manifest in the preëxisting lesion. Those were forms showing pronounced healing tendencies, with a favorable outcome of the disease as a whole, in a number of instances.

The following 2 cases are cited as examples of massive posthaemoptysis pneumonic lesions, the first illustrating the resolving, the second the progressive form:

Case 6,659: L. K., a white woman, aged 25, was admitted to the Tuberculosis Service of the Metropolitan Hospital on October 16, 1932. Three years before admission she had had haemoptysis on one occasion. However, she remained in good health until July, 1932, when she had a number of haemoptyses of moderate severity. Following this, she developed fever, chills and dyspnoea. Roentgen examination of August 3, 1932 (figure 3A) revealed a massive pneumonic lesion occupying the lower two-thirds of the right lung, and there was an area of exudative infiltration in the upper third. There

FIG. 4A

FIG. 4B

FIG. 5A

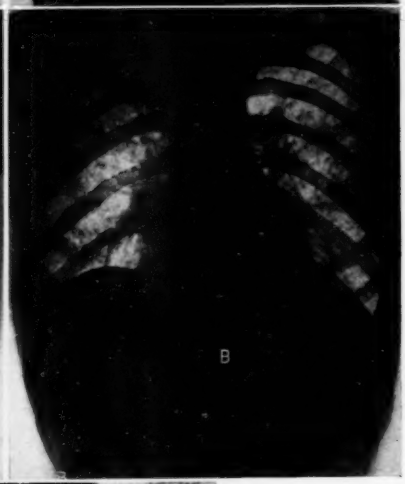

FIG. 5B

FIG. 5C

were no signs which would indicate massive atelectasis of the lung. The sputum was positive for tubercle bacilli. The acute symptoms subsided after a short time, and on admission to this hospital the patient had very few complaints. Examination of the chest revealed dulness over the right upper lobe. The breath-sounds were bronchovesicular, and there were scattered moist râles throughout the right lung. Roentgen examination of October 20, 1932 (figure 3B) demonstrated that the massive lesion in the right lung had undergone marked clearing. However, diffusely disseminated soft foci throughout the entire right lung could still be seen. During the subsequent course the patient's condition improved. The temperature remained within normal, and the sputum became persistently negative. Follow-up roentgen studies over a period of seven months revealed that the focal dissemination in the right lung remained stationary. The patient was discharged on July 3, 1933.

Case 11,950: C. C., a man, Negro, aged 22. His past history was not quite definite. It appeared, however, that he had had some symptoms referable to the respiratory tract for several years. In May, 1935, he developed a marked cough and expectoration followed by a number of haemoptyses. Roentgen examination shortly afterward, on May 13, 1935 (figure 4A) disclosed a large cavity in the right upper lobe and coalescent bronchopneumonic patches through the remaining portions of the right lung, especially at the base. The left lung was entirely clear. On June 5, 1935, the patient was transferred from another institution to Sea View Hospital. At the time of admission he appeared acutely ill. He was markedly dyspnoeic, his pulse was rapid and his temperature ranged between 102° and 103°. Examination of the chest revealed dulness on the right side from the apex to the base. There were signs of cavitation in the right upper lobe and numerous coarse moist râles throughout the right lung. The sputum was persistently blood-streaked and contained numerous tubercle bacilli. There was evidence of a progressive spread of the lesion on the right side as indicated by the roentgen examination of June 11, 1935 (figure 4B), which demonstrated progressive excavation in the upper lobe and massive pneumonic involvement throughout. The left lung showed a moderate number of soft foci in the midportion. The patient declined rapidly, and he died on June 14, 1935, about six weeks after the onset of the recent acute phase of his illness. The postmortem examination revealed a number of interlocking cavities filled with blood-clots occupying the superior portion of the right upper lobe. There were massive caseous pneumonic changes throughout the right upper, middle and lower lobes, the foci varying in size from miliary to acinous, coalescent acinous and lobular patches. The intervening lung tissue showed perifocal inflammation and oedema. The left lung contained a moderate number of scattered caseous foci.

3. Diffuse Focal Disseminations

This is the most frequent type of pulmonary changes observed after haemoptysis. In the group of cases studied here, two-thirds presented the characteristic features of this form. Great variations in the extent of such lesions probably occur, ranging from a small number of foci to a diffuse dissemination throughout the lungs. However, only instances of the latter type were included in this series, as changes due to a limited spread could hardly be distinguished from a spontaneous extension of the disease as commonly seen in the progressive forms of pulmonary tuberculosis.

As in the preceding group, the most significant point is a differentiation of the lesions according to their subsequent evolution and fate. In the predominant majority of the cases of this group, the acute dissemination following haemoptysis caused a more or less rapid progression of the tuberculous lesion and resulted in an eventual fatal outcome. There was only a comparatively small number of patients in whom the disseminated spread proved to be of the evanescent type and in whom the subsequent clinical course was favorable. In a few cases the subsequent course remained fairly stationary in spite of the persistence of the widely disseminated spread in the lung.

The initial clinical manifestations are, as a rule, quite identical in all cases of diffuse posthaemoptysis dissemination, irrespective of the subsequent development of the changes. The constitutional signs and symptoms as well as the physical findings do not differ much from those observed in cases with massive infiltration. However, the cases in which the diffuse dissemination is of the benign and evanescent character usually show a rapid disappearance of the acute manifestations. Persistence of the toxic symptoms, on the other hand, indicates that an extensive and progressive spread of the tuberculous process has been brought about by the haemoptysis.

The roentgen findings consist in a diffuse dissemination of soft foci of small but unequal size which frequently show an irregular distribution. In the majority of cases the involvement was bilateral. There were only few instances in which the spread was limited to one lung. In most cases the changes are much more extensive on that side which shows evidence of a preëxisting chronic lesion. In the contralateral lung the distribution of the spread shows great variations, ranging from a small number of foci to a diffuse involvement in some instances.

Cases in which the original lesion is situated in the right lung frequently show involvement of the dependent portions of the contralateral lung, in addition to the diffuse dissemination through the same side. In lesions situated on the left side, on the other hand, the reverse could be frequently observed, that is, a diffuse dissemination through the left lung and involvement of the upper lobe of the right lung. These dissimilarities in distribution of the spread are evidently due to the difference in the anatomical course of the lobar branches of the bronchi, as between the right and left side. The mode of distribution of the lesions resulting from aspiration is probably also influenced by the position in which the patient remains during the period following the haemoptysis.

What has been said regarding the similarity of the immediate clinical picture in the benign and progressive types of spread applies to an equal extent to the early roentgen findings. One could hardly venture any prediction as to the subsequent course from the morphological character and from the extent of the dissemination. On the basis of serial follow-up studies, however, a differentiation between the favorable and progressive forms of spread will be possible in most instances, provided, of course, that the period of observation extends over a sufficient length of time. In the benign types there can be noted a gradual decrease in the extent of the changes. The process of resolution is not a rapid one, it usually extends over a period of many months and complete absorption of the changes is only rarely observed. In most instances there remain more or less marked traces of the preceding widespread dissemination. Those foci which persist assume the character of discrete nodules of the chronic productive type. The clinical improvement takes place much more rapidly than the roentgenographic evidence would indicate, and it is not at all unusual to find the patient entirely symptom-free while the roentgenogram still reveals the presence of quite marked changes.

In the unfavorable forms of disseminated spreads, the follow-up roentgen-ray studies reveal a progressive increase in the extent of involvement. The individual foci become larger in size, frequently showing confluence into larger pneumonic patches; they retain the soft character and their borders remain ill-defined. These lesions in turn may give rise to further dissemination, and eventually there results a diffuse and massive spread in which both lungs are riddled with an enor-

mous number of foci. The total duration of the disease in such cases varies between a few weeks and several months. In some instances the course is quite acute, and the fatal termination occurs within a very short time as a result of an unusually massive spread. The majority of cases, however, run a subacute but distinctly progressive course which extends over a period of several months. It is extremely difficult for any form of therapy to influence the progressive nature of the disease in these cases. The widespread and bilateral extent of the spread prevents the application of proper and effective collapse therapy measures in the majority of these instances. In some cases in which the spread is strictly or predominantly unilateral, a timely collapse of the involved lung by means of pneumothorax may prove of value.

As regards the correlation between the type of the preëxisting pulmonary lesion and the fate of the posthaemoptysis spread, it should be mentioned that the observation cited in an earlier paragraph holds true to an equal extent for this group of cases. Thus, progressive types of spreads were practically always derived from lesions of an essentially similar nature. The favorable evolution, on the other hand, could be seen in those instances in which the original lesion was of a comparatively benign character, as in the resolving exudative and in the chronic stationary fibrocaseous forms. It seems of particular value that this behavior could also be observed in this group, which comprises the bulk of the entire series.

It is evident that the posthaemoptysis lesions of this type are due to a diffuse bronchogenous dissemination resulting from aspiration. In cases with a clinically progressive course, the pathologicoanatomical findings are essentially of the same nature as those found in the corresponding form of massive posthaemoptysis infiltrations, the caseopneumonic changes being the predominant feature. The difference lies mainly in the extent of the lesion and in the manner of its distribution. These in turn are probably determined by the calibre of the bronchi from which the involvement extends into the lung parenchyma. In contrast to the massive caseopneumonic lesions of the preceding group, the changes found in the disseminated types consist in a widespread distribution of acinous and subacinous lesions, with occasional coalescence into sublobular or lobular pneumonic foci. Because of the presence of perifocal inflammatory zones, the size of the individual foci appears considerably larger in the roentgenogram than the anatomical

findings seem to indicate. Ulceration and formation of multiple small cavities may be found in cases in which the spread had existed for some time before the patient died.

The exact nature of the anatomical changes which cause the clinically benign and evanescent form of posthaemoptysis focal dissemination is not definitely established. Because of their favorable course the answer to this question must, of necessity, be largely conjectural since it is not based on actual postmortem observations. It is very probable, however, that the nature of the changes which take place here is quite similar to those referred to in the discussion of the resolving forms of massive infiltrations, the difference being merely in the degree of involvement and in the type of distribution. Disseminated nonspecific bronchopneumonic foci and areas of atelectasis may, to some extent, account for the early roentgenographic changes in such cases, and may well explain their favorable evolution, as such lesions are capable of complete resolution. However, the fact that the process of absorption usually extends over a considerable time, and that in most instances there can be found persistent disseminated nodular foci, are points which indicate a spread of tuberculous origin. The roentgenographic appearance of such residual changes, in conjunction with the favorable clinical course, suggest that, following the absorption of the initial exudative reaction, there remain predominantly productive foci of a stationary character, which generally do not result in clinical progression of the disease.

The diffuse focal lesions resulting from haemoptysis may show certain roentgenographic similarities with haematogenous disseminations. However, in the early phase of the spread, and especially in the progressive forms, this differentiation is, as a rule, not difficult. The unequal distribution, the morphological characteristics of the individual foci, as indicated before, the almost invariable coexistence of a caseocavernous lesion in the lung, and, above all, the history of a preceding recent haemoptysis, are important points in favor of the bronchogenous origin of the spread. In the more stationary chronic forms of posthaemoptysis dissemination, the differentiation from chronic haematogenous lesions, of the type described elsewhere (13), is not always simple. This is especially the case if the patient is seen after a considerable interval has elapsed since the occurrence of the haemoptysis, and serial roentgen-ray studies are not available. In the cases in which the posthaemoptysis spread assumes a chronic character the foci become more discrete; they are larger and more numerous in the upper fields,

thus giving the impression of a symmetrical lesion which diminished in the craniocaudate direction. This appearance is probably due to the fact that absorption of the initial exudative changes is more pronounced in the basal portions of the lungs. These morphological features, in conjunction with the relatively benign clinical course, account for the difficulties in distinguishing such instances of posthaemoptysis spreads from the chronic and benign haematogenous lesions. On the other hand, a strictly or predominantly unilateral diffuse focal dissemination is an important indication of a bronchogenous lesion and should suggest the possibility of a posthaemoptysis aspiration as the cause of the spread.

The following two cases may serve as examples of the progressive type of a diffuse focal dissemination:

Case 3,926: A. Y., a white man, aged 23, was admitted to the Metropolitan Hospital on June 2, 1930. He had been in good health until several weeks before admission, at which time he presented clinical evidence of an active tuberculous process in the lung; and a roentgenogram of June 3, 1930 (figure 5A) revealed an apparently recent exudative lesion in the superior portion of the right upper lobe with probable breaking-down. The remaining lung fields were clear. The sputum was positive for tubercle bacilli. Between June 7 and June 9, 1930, the patient had several haemoptyses of moderate severity. This was followed by an aggravation of the constitutional signs and symptoms. Röentgen examination of June 24, 1930 (figure 5B) revealed a diffusely disseminated soft focal spread throughout both lungs with the exception of the superior portion of the left upper lobe. The temperature was persistently elevated up to 102°; there was progressive dyspnoea and physical signs indicated an extensive spread of the lesion. On September 17, 1930, the roentgenogram (figure 5C) showed marked progression of the disseminated focal spread with coalescence into larger patches. The patient's condition became progressively worse, and he died on November 24, 1930, about five months after the occurrence of the spread. Postmortem examination revealed a widespread caseopneumonic process in both lungs with innumerable foci of acinous, sublobular and lobular size, and a number of small cavitations, chiefly in the right upper lobe.

Case 5,343: N. B., a Negress, aged 32, was admitted to the Metropolitan Hospital on January 25, 1935. Her history indicated a recent onset of illness, and the roentgenogram of January 26, 1935 (figure 6A) revealed an exudative and cavernous process in the right upper lobe; the remaining lung fields were clear. Her temperature was elevated to 101°, and her sputum contained

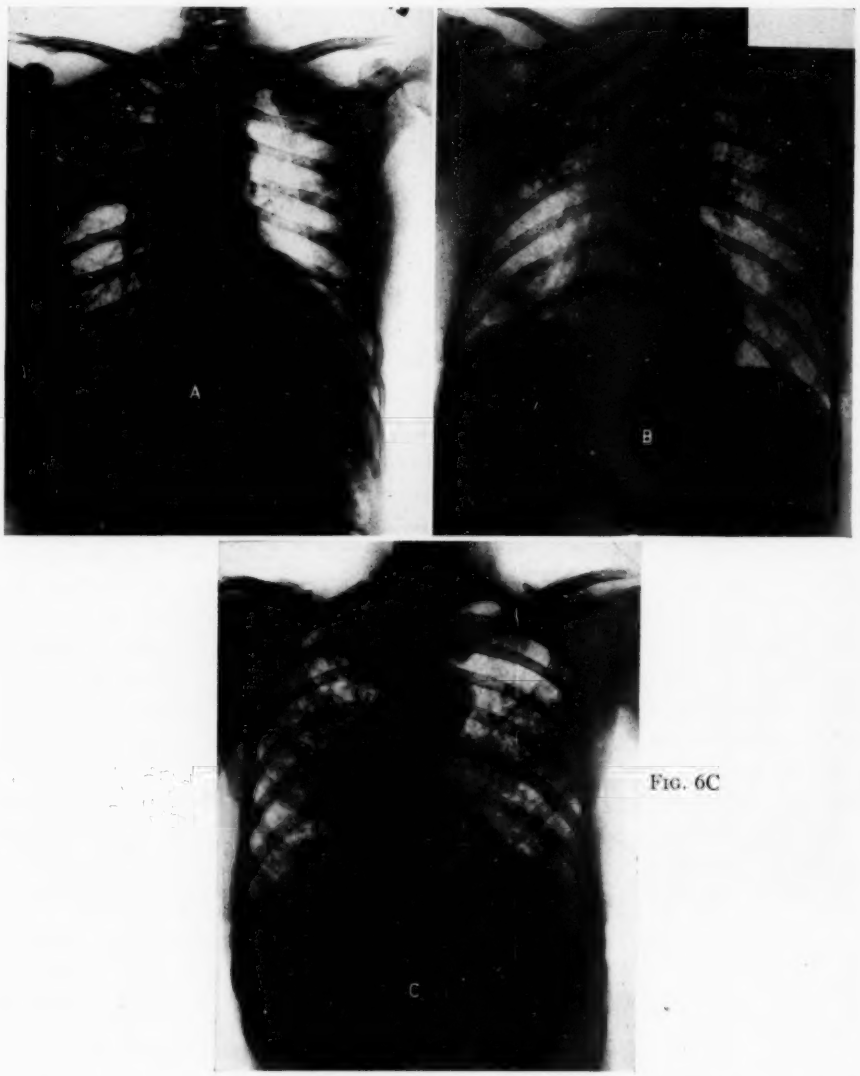

FIG. 6A

FIG. 6B

FIG. 6C

FIG. 6. Roentgenogram of January 26, 1935 (A) revealed a caseopneumonic lesion in the right upper lobe with cavitations. There were no other abnormal findings in the lungs. On April 11, 1935 (B), several days after a series of haemoptyses, there was diffuse dissemination of soft foci in both lungs and on May 4, 1935 (C) there was extensive progression of the lesion.

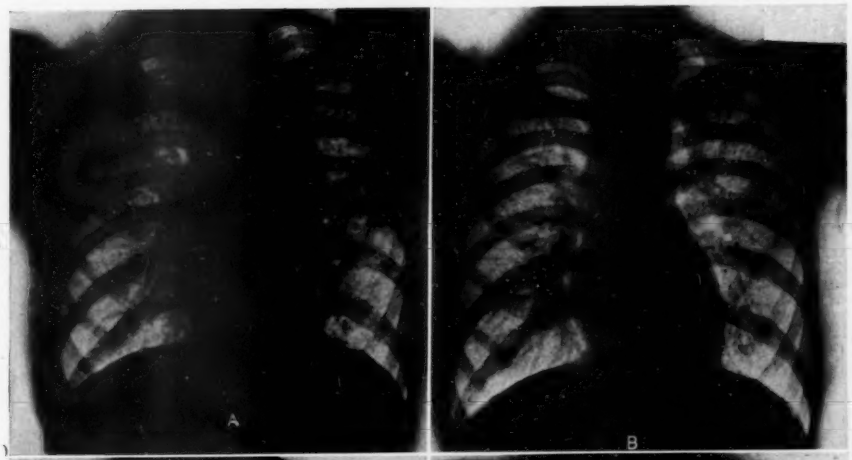

FIG. 7A FIG. 7B

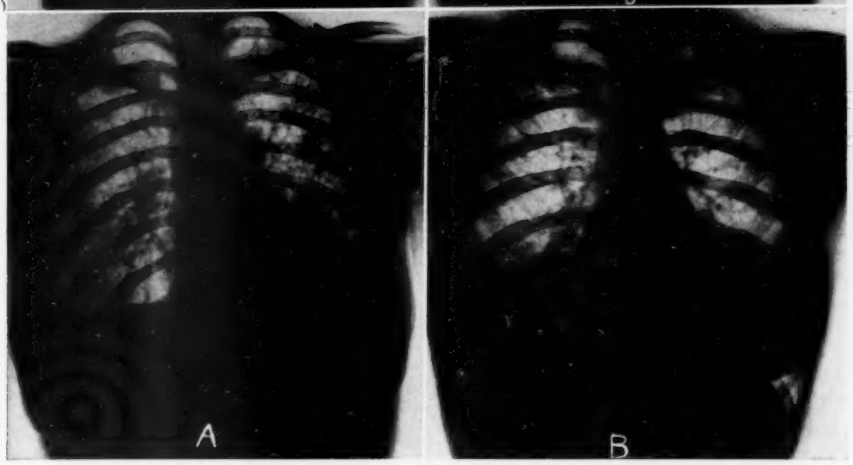

FIG. 8A FIG. 8B

FIG. 7. Roentgenogram of February 6, 1931 (A) showed diffusely disseminated soft foci throughout the left lung and in the right upper lobe following a number of haemoptyses. On July 11, 1931 (B) marked clearing of the focal spread could be seen. There were residual discrete nodular foci in both lungs.

FIG. 8. Roentgenogram of June 19, 1931 (A), after a recent haemoptysis, showed disseminated soft foci through the left lung and in the right upper lobe. A small cavity could be seen at the level of the left clavicle, not clearly visible in the reproduction. Follow-up roentgenogram of November 13, 1933 (B) revealed marked clearing of the disseminated spread. The character of the remaining changes suggested a chronic productive type of lesion in both upper lobes.

numerous tubercle bacilli. Repeated attempts to collapse the right lung by means of pneumothorax were unsuccessful. Between April 2 and April 9, 1935 she had a number of haemoptyses ranging between 4 and 10 ounces of blood. Roentgen examination on April 11, 1935 (figure 6B) disclosed a diffuse soft focal spread throughout both lungs. The patient's condition grew steadily worse. She continued to run a highly toxaemic course, developed progressive dyspnoea; and a follow-up roentgenogram on May 4, 1935 (figure 6C) showed extensive progression of the lesion. She died on May 15, 1935, five months after the onset of her illness and about six weeks after the occurrence of the haemoptyses which brought about the rapid spread of the disease. The postmortem examination revealed a chronic caseocavernous process in the right upper lobe and numerous caseous foci diffusely spread throughout both lungs, varying in size from acinous to lobular.

The following cases illustrate the resolving form of the disseminated focal spread:

Case 4,454: H. H., a man, aged 23, Negro, was admitted to the Metropolitan Hospital on January 23, 1931. During a period of three months preceding the admission he had had profuse haemoptyses on a number of occasions. At the time of admission he did not appear severely ill, the temperature was only slightly elevated, and after several days it became normal. Examination of the chest revealed numerous fine and medium moist râles throughout the left lung and few râles over the right upper lobe. A roentgenogram of February 6, 1931 (figure 7A) showed a diffuse dissemination of soft foci through the entire left lung and the right upper lobe; in the left infraclavicular region there could be seen a patch of exudative infiltration. The sputum contained a moderate number of tubercle bacilli. On further observation the patient showed steady improvement; he became practically symptom-free and left the hospital on July 11, 1931. Serial roentgen-ray examinations revealed progressive clearing in both lungs. The roentgenogram of July 11, 1931 (figure 7B) showed residual focal dissemination of a discrete nodular character. The appearance of the lesion in the left infraclavicular region suggested chronic fibroindurative changes.

It may be of interest to add that this patient returned to the hospital one year later following another haemoptysis, which gave rise to a renewed spread in the lungs. After several months, resolution of the changes could again be observed. His general condition was satisfactory, the sputum became negative, and he was discharged on January 28, 1933, two years after his first admission.

Case 4,800: S. M., a white girl, aged 17, was admitted to the Metropolitan Hospital on June 19, 1931. Her illness began three weeks before admission to the

hospital with a productive cough followed several days later by an haemoptysis of moderate size. At the time of admission she appeared fairly comfortable; her temperature, pulse and respiration were within normal. Examination of the chest revealed altered breathing and moist râles over the left lung. The sputum was positive for tubercle bacilli. Roentgen examination on June 19, 1931 (figure 8A) revealed diffusely disseminated soft foci throughout the entire left lung and a moderate spread in the right upper lobe. A small cavity could be seen on the left side at the level of the clavicle. On rest in bed the patient did very well and the sputum became negative. After two months she was transferred to a country sanatorium in excellent condition. Follow-up roentgen examination on November 13, 1933 (figure 8B), twenty-seven months after discharge from the hospital, showed marked clearing of the disseminated spread. There remained, however, discrete nodular foci scattered in both upper lobes. The cavity could not be seen. The patient appeared to be in good health and had no symptoms whatever.

DISCUSSION

The question arises: What is the causative connection between the haemoptysis and the development of the pulmonary changes such as described here; or, in other words, to what extent is the aspiration of blood responsible for the production of such changes? The results of the experimental work of Austrian and Willis (14) indicate that the presence of blood in the aspirated material does not constitute an essential factor in the development of the posthaemoptysis lesions in the lungs. In rabbits previously infected with tuberculosis, these authors obtained the identical pulmonary changes after intratracheal injections of suspensions of either tubercle bacilli or old tuberculin, no matter whether blood was or was not added to the suspension. These changes were analogous to those found in roentgenograms of patients after haemoptysis and were considered as due to a specific allergic reaction. Similar injections of blood alone, on the other hand, did not result in pulmonary changes comparable to those obtained after injections of suspensions of either tubercle bacilli or tuberculin.

These experimental data lend support to the clinical observations as related in this report, which suggest that the pulmonary lesions developing after haemoptysis are largely the result of an extension of the tuberculous process. They are evidently caused by aspiration of tubercle bacilli and their toxic products. The importance of the haemoptysis lies in the fact that its occurrence provides particularly favorable opportunities for acute aspiration. The shallow respirations and the

impaired ventilation of the lung during the period following the haemoptysis, due partly to the patient's state of anxiety and partly to the prolonged recumbent position, are important factors promoting the occurrence of aspiration. An additional factor is the action of the all too frequently administered narcotics, especially morphine, their inhibitory effect on the respiratory centres, and the suppression of the cough reflex. The frequent occurrence of aspiration is thus to be expected and clinical observations indicate that aspiration of greater or lesser extent is a very common accompaniment of haemoptysis. However, only in a fraction of these cases are demonstrable pulmonary changes found. This is evidently due to the fact that the mere aspiration of a moderate quantity of blood has no deleterious effect. The presence of aspirated blood in the bronchial tree hardly gives rise to any demonstrable changes in the roentgenogram. This is in agreement with the observations of Jagoda (15) and Fleischner (16).

The conditions created by the haemoptysis and the resulting aspiration thus pave the way for a spread of the tuberculous lesion, as they facilitate a sudden distribution of tubercle bacilli over wide pulmonic areas. To be sure, this occurrence is not infrequently attended by a simultaneous development of pulmonary changes of a nonspecific nature. This applies particularly to lesions of a transient and evanescent character, such as massive or patchy atelectasis, or ordinary aspiration bronchopneumonia of variable extent, which as a rule clear up quite rapidly. However, clinical and roentgenographic follow-up studies indicate that cases showing a rapid and complete resolution of the pulmonary changes resulting from haemoptysis are rather uncommon. In the predominant majority of instances the character of the lesions indicates an extension of the tuberculous process.

The preceding analysis of the various forms of posthaemoptysis complications revealed wide dissimilarities of the resulting pulmonary changes, particularly with respect to their subsequent evolution, ultimate fate and influence on the course of the disease as a whole. There were numerous gradations, ranging from lesions of a benign character, which showed marked clearing followed by clinical recovery, to very severe and acutely progressive forms with rapidly fatal outcome. What are the factors responsible for these marked variations in the behavior of such spreads?

An inquiry into the question of whether the severity and the number of haemoptyses have a direct influence on the extent and severity of the

resulting lesions did not disclose any definite relationship. There were cases in which an apparently moderate haemoptysis was followed by very extensive and progressive changes, while in numerous other instances no demonstrable pulmonary lesions could be seen after profuse haemoptyses. The question was also considered as to whether the presence or absence of a preëxisting cavitation, which could be looked upon as the source of the haemorrhage, might not be the deciding factor as regards the fate of the resulting changes. This likewise failed to provide a satisfactory explanation, since, with only few exceptions, demonstrable cavities were present in all cases studied in this series, and yet the subsequent evolution of the changes was so vastly different. There could be observed, however, a definite parallelism between the general character of the preëxisting pulmonary lesion and the subsequent behavior of the spread, which indicates that the evolution and the ultimate fate of the posthaemoptysis changes is determined largely by the nature of the original disease. As was pointed out in the discussion of the individual types of the posthaemoptysis spreads, the severest and most progressive forms of involvement are found in those cases in whom the original lesion is of the predominantly exudative-caseous character with progressive destruction. The chronic protracted course and the benign evolution of the lesions resulting from diffuse aspiration are, as a rule, observed in those instances in which the preëxisting lesion is of a corresponding character. The manifestations of spontaneous healing frequently seen in these cases, such as absorption of the exudative infiltration and the subsequent fibrosis which result in self-limitation and localization of the disease, represent characteristic features of both the original lesion and of the secondary spread and account for the favorable clinical course.

This correlation points in the first place to the infective dose as the important factor which determines the evolution and the fate of the posthaemoptysis spreads. It is obvious that a sudden flood of a massive dose of tubercle bacilli into the bronchial tree will lead to acute and progressive widespread lesions, whereas smaller doses will result in correspondingly less severe sequelae. It should be mentioned, of course, that other factors, such as variable states of allergic response and immunity, probably have an important bearing on the evolution of the resulting changes, inasmuch as they may influence the effect of the spread in a favorable or in an unfavorable manner. However, our knowledge regarding the influence of these factors is as yet not suffi-

ciently accurate to permit their proper appraisal from a clinical standpoint.

The prognostic significance of the pulmonary changes resulting from haemoptysis and their influence on the eventual outcome of the disease as a whole cannot be properly evaluated unless such cases are followed for a sufficient length of time. As stated at the outset of this paper, no satisfactory statistical analysis of the general incidence of posthaemoptysis pulmonary changes has been attempted. It seems pertinent, nevertheless, to submit some data obtained in a group of cases in which the sequence of events could be considered as sufficiently characteristic, and in which the evolution of the lesions as well as the ultimate results could be closely studied. In this group of 90 patients, there were sixty in whom widespread changes of a distinctly progressive nature had been brought about by haemoptyses. Of these, fifty-five died during the course of observation. In thirty-five death occurred within three months after admission to the hospital, in eight between three and six months, and in eight between six and twelve months after admission. The average duration of illness for this group, from the occurrence of the haemoptysis until the fatal termination, was five months.

A comparison of these figures with the mortality rates of the total number of patients admitted during the same period revealed that the former far exceeded the latter, notwithstanding the fact that the general mortality rate in this institution is very high owing to the predominance of cases with advanced and progressive lesions. It must be admitted, of course, that a comparison between two numerically so widely divergent groups has its distinct limitations, and therefore does not permit an accurate statistical evaluation. Nevertheless, it seems reasonable to state that such figures indicate the deleterious effect of the posthaemoptysis spread on the subsequent course of the disease, and they illustrate the hazards with which this occurrence is fraught. The term "galloping phthisis" seems best exemplified by such cases of rapidly progressing lesions resulting from haemoptysis, and it is very probable that this complication is an important cause of such acute and almost invariably fatal forms of pulmonary tuberculosis.

It was deemed necessary to emphasize here the unfavorable results of posthaemoptysis aspiration in view of some statements in the literature which show a tendency to minimize the effect of this occurrence on the subsequent course of the disease. Fishberg (17) states that "hemoptysis has no influence on the course and prognosis of the disease in the

vast majority of cases," and that, "the fear of a spread of the lesion is without sound foundation." Cardis (18) and Thoyer (19) recently stressed the benign nature of the disseminated focal spreads occurring after haemoptysis. Stivelman (6) believes that such changes are due to atelectasis of various degrees resulting from aspiration of blood and that they clear rapidly. Such conclusions are evidently the result of observations based on a limited number and a particular type of cases. They may also be accounted for by a lack of opportunity for a follow-up study of the subsequent development and of the ultimate fate of the pulmonary changes. It would be equally misleading, of course, to advocate the opposite view by putting undue emphasis on the unfavorable sequelae of posthaemoptysis aspiration. In the present report the attempt was made to avoid such generalizations, as it was stressed that the clinical significance of these changes and their effect on the evolution of the disease, as a whole, depend primarily on the character of the original lesion in the individual case. This, incidentally, illustrates the importance of a qualitative differentiation of the various forms of pulmonary tuberculosis in general, a point which was particularly emphasized in the clinical classification suggested by Ornstein (20).

The foregoing considerations indicate that, from a therapeutic standpoint, our foremost aim must be the elimination of those factors which promote the occurrence of aspiration. The ill effects of the injudicious administration of narcotics, especially of morphine, have already been referred to in an earlier paragraph. One also has to question the expediency of placing the patient at complete rest in the recumbent position. It would seem more appropriate to promote expectoration and ventilation by change of posture, thereby giving the patient a better chance to counteract the effects of aspiration.

It is not intended here to enter into a detailed discussion of the treatment of haemoptysis. There are some points, however, which should be mentioned in connection with the application of artificial pneumothorax as a therapeutic measure for pulmonary haemorrhage. This procedure is of value in the attempt to control the bleeding, and, if employed early, may prevent an extension of the disease process in the lung. This applies particularly to the cases in which the original pulmonary lesion is of a progressive and destructive nature and in which the results of aspiration following haemoptysis are frequently of a serious character. In suitable cases the pneumothorax treatment should, of course, be continued as a curative measure. Roentgen examination immediately

after the occurrence of the haemoptysis and follow-up studies at frequent intervals are of inestimable value in depicting the extent and the subsequent stages of development of the resulting changes. This may be carried out without hesitation and, as a rule, does not cause any discomfort to the patient. In most instances the roentgenogram indicates the situation of the source of the haemorrhage by demonstrating the presence of cavitation. The determination of the side from which the bleeding occurred is of particular importance in cases in which the application of pneumothorax is considered. Although posthaemoptysis spreads are frequently bilateral, one will but rarely encounter serious difficulties in determining the source, as the changes resulting from aspiration are almost invariably much more extensive on the side where the original lesion is situated. A consideration of this differential point is also helpful in cases with bilateral cavitations.

SUMMARY AND CONCLUSIONS

1. The changes occurring in the lungs following haemoptysis in pulmonary tuberculosis were studied, with particular reference to their subsequent evolution and influence on the course and prognosis of the disease.

2. An attempt was made to define the types of posthaemoptysis pulmonary complications according to their clinical and morphological features. The main forms to be distinguished are atelectasis, massive pneumonic lesions and diffuse focal disseminations. Particular emphasis was placed on the differentiation of the resolving and clinically benign forms from lesions of a progressive and prognostically serious nature.

3. Follow-up studies of the subsequent evolution of the posthaemoptysis pulmonary lesions indicate that in the predominant majority of the cases these changes are due to a spread of the tuberculous process. Coexisting nonspecific changes of various degrees, resulting from aspiration, probably account to some extent for the findings observed during the early period after the occurrence of the haemoptysis, especially in the resolving forms of pulmonary complications.

4. There could be found a distinct correlation between the character of the preëxisting pulmonary lesion and the fate of the posthaemoptysis spread. The evolution, and hence the prognostic significance of the spread are largely determined by the nature and severity of the original pulmonary lesion.

5. Haemoptysis in pulmonary tuberculosis represents a distinct potential hazard, as it not infrequently gives rise to extensive spreads of the

pulmonary lesion of the type of "galloping phthisis"; this is especially the case in those instances in which the preëxisting lesion is of the progressive and destructive caseous-cavernous character.

6. The therapeutic management of haemoptysis must take into account the possibility of pulmonary complications, and efforts should be directed toward the elimination of those factors which are apt to promote the occurrence of aspiration.

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PULMONARY TUBERCULOSIS AND GENERAL PARESIS

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Before going into the subject of coexisting pulmonary tuberculosis and general paresis it might be well to consider briefly the status of syphilis in general among the tuberculous. That such widespread diseases should not infrequently occur together is not at all surprising. The percentage of syphilitics among the tuberculous is variously estimated by different observers: thus, to cite a few figures from the very extensive literature, Sullivan in 1931 in a review of the subject found it to vary from 3 to 19 per cent, while in his own series of 1,000 cases of pulmonary tuberculosis definitely proved by sputum examinations, X-rays, physical findings, and some with diagnostic tuberculin, Sullivan reported 11.6 per cent as syphilitic. Barksdale (of the Veterans Administration) reported that 2.2 per cent of 9,045 whites and 12.6 per cent of 563 Negroes with tuberculosis gave positive Wassermann, Kahn or Meinecke reactions. Gallant obtained positive Wassermann reactions in 21 per cent and positive Kahns and 15 per cent in his series; and he feels that in tuberculosis the Kahn test is more reliable, the Wassermann giving a certain number of false positives. These figures serve to indicate the extent, and consequently the importance of the combination of the two conditions. Opinions differ widely as to the interrelationship of syphilis and tuberculosis. Sullivan states that syphilis coincident with tuberculosis has shown a decidedly unfavorable influence on the tuberculosis in direct proportion to the extent and activity of the tuberculosis. D'Orszagh holds similar views; he quotes Neumann, who in 500 syphilitics (postmortem) found that 10.6 per cent died of pulmonary tuberculosis, and he mentions another series of 698 syphilitics in which 26.67 per cent died of tuberculosis and only 22.5 per cent succumbed to syphilis. D'Orszagh further cites Sergent, Zappia and Raitz, who emphasize the frequency of pulmonary tuberculosis in congenital syphilis, while Epstein and Pertik Otto find the incidence much less frequent and observe a favorable influence of syphilis on tuberculosis. Finally, just to indicate still another standpoint, Beck says, "Neither the sphilitic

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possesses a particular susceptibility to tuberculosis nor the tuberculous individual to syphilis; nevertheless when both diseases meet in the same individual the course of one or the other or often of both is more severe than the ordinary run of case." There is just as wide a diversity of opinion concerning the treatment of the syphilitic with tuberculosis. Some of the earlier observers did not attempt to treat syphilis at all in the presence of active pulmonary tuberculosis. However, the question at present is rather as to the type and manner of administration of antisyphilitic treatment as well as the selection of cases. Stokes says that "with complicating active tuberculosis the tuberculosis requires the more immediate and elaborate attention; if the syphilis is recent and active, treatment may be imperative to protect contacts." Stokes feels that both diseases benefit by antisyphilitic treatment and observed but one example of lighting up of tuberculosis by antisyphilitic treatment and many of the reverse, that is, an improvement of tuberculosis by such treatment. He believes that iodides should not be used.

Sullivan believes that patients with both diseases benefit by antisyphilitic treatment, but he recommends small doses of the arsenicals (not over 0.40 gm. of neoarsphenamin) and warns against the use of iodides. Gallant, who has obtained good results in treating syphilis, even in the presence of active far-advanced-B pulmonary tuberculosis, also emphasizes the importance of using small doses of arsenic. Habliston and McLane report a decrease in mortality and an increase in improvement of pulmonary tuberculosis when the syphilis was treated by arsenicals. They quote Mouradian, who believes, on the other hand, that arsenic is contraindicated and that potassium iodide should be used. Kennedy and Lee report good results in a small group of cases of pulmonary tuberculosis complicated by syphilis (three with positive spinal fluid), who received antisyphilitic treatment, but warn against such treatment in spreading an exudative tuberculosis. Fishberg feels that bismuth is safer than arsenic; he says however that in tertiary syphilis iodides should be used, particularly in old fibroid tuberculosis. Turner, at the Municipal Tuberculosis Sanitarium of Chicago, Illinois, avoids antisyphilitic treatment in exudative, spreading tuberculosis or in the presence of haemorrhage, and is now using a bismuth preparation almost exclusively. Fisher obtained good results in tuberculous patients who were receiving pneumothorax treatment or who had undergone phrenic-nerve resection; he concludes that such collapse therapy is not appreciably affected by antisyphilitic treatment.

The foregoing merely illustrates the vast amount of discussion aroused by the problem of treating syphilis in the presence of tuberculosis. The consensus of opinion as to treatment at present appears to be that such treatment should be carried out, observing the contraindications mentioned (including such others as complicating cardiac and renal diseases), that the dosage of arsenicals be reduced and that iodides in general be avoided.

While the literature on the subject of coexisting syphilis in general and pulmonary tuberculosis as indicated above is quite exhaustive, the coexistence of pulmonary tuberculosis and general paresis does not seem to have received very much consideration. D'Orszagh quotes Schreiber as stating that changes in the nervous system occur less frequently in tuberculous syphilitics than in patients with syphilis alone. In 1909 Rosanoff in New York reported in a postmortem study of 214 paretics, 6 cases of active pulmonary tuberculosis, 8 of quiescent and 33 of healed, while of 842 other psychotics who came to autopsy there were 195 with active pulmonary tuberculosis, 21 quiescent and 153 healed. Rosanoff feels that paretics exhibit a heightened immunity against tuberculosis. In 1919 Elkins and Thomson in England reported that of 52 paretics, who died between January 1, 1914 and December 31, 1918, 16 were found to have some tuberculosis, based on postmortem examination for the most part. No further details concerning the type or extent of the tuberculosis is given. They state that in the great majority of cases of tuberculosis among the insane the classical symptoms are absent, that there is very little cough and expectoration and that frequently gross pulmonary lesions exist without any corresponding physical signs. McGhie and Brink of Toronto in 1934 reported 8 cases of pulmonary tuberculosis in paretics, among a total of 186 cases of pulmonary tuberculosis in all psychoses. They report, for example, a much larger percentage of tuberculosis in the dementia-praecox group. They emphasize the difficulty of physical examination and also recommend X-ray study just as do Elkins and Thomson. MoGatti, Spiller and Luchi report one case of general paresis, tertiary syphilis and pulmonary tuberculosis, in which malaria therapy was administered in December, 1932, and the patient was reported as improved in January, 1933. In June, 1932, he had had an amputation of the lower third of the left thigh for gangrene following an obliterative endarteritis. The extent of the tuberculosis was not described, but the sputum was negative. The case is discussed chiefly from the standpoint of the rarity

of tertiary syphilis (except syphilitic aortitis) and general paresis, the tuberculosis apparently being a lesser consideration except in so far as it affected the general condition of the patient.

In view of the above it was felt that it might be of interest to report a group of 11 cases of coexisting paresis and pulmonary tuberculosis. While this group of cases is so small that it would be difficult to draw any conclusion concerning the coincident relations of tuberculosis and paresis, it seems worth mentioning that of 255 cases of paresis (including recent discharges) there were 7 cases of pulmonary tuberculosis; and that, of 222 cases who are at present in the hospital, there are 5 cases of pulmonary tuberculosis. Of 147 patients discharged, by death or otherwise, from 1927 to 1933, there were 5 cases of unquestioned pulmonary tuberculosis (which are also reported here) and 4 others which are not included in this series because of insufficient data concerning pulmonary tuberculosis. However, these cases are principally cases of minimal arrested tuberculosis, and it is readily understood that such cases would be difficult to demonstrate and yet have an appreciable effect on any percentage figures.

Although this series of cases is small, some have been under the observation of the Veterans Administration for many years and the information is fairly complete. The case histories follow:

Cases

1: C. L., white, male, aged 34, admitted September 24, 1930, and still in the hospital (September 15, 1935). He first came under our observation in January, 1920, when a diagnosis of pulmonary tuberculosis, involving the right upper lobe was made, based on X-ray, physical findings and history. Sputum negative. Gave history of initial infection sometime in 1920, for which he received injections for about one year but does not know what the drug was. In August, 1921, while undergoing tuberculosis treatment, a blood Wassermann was positive. Mental symptoms appeared in November, 1929, and on January 17, 1930, a diagnosis of general paresis was made. Accordingly taken to a state hospital, where blood Wassermann and Kahn were 4-plus; spinal-fluid Wassermann 4-plus; and gold curve 5444311000. In March and April of 1930, received 12 diathermy heat treatments, and from September to December, 1930, 10 injections of tryparsamide, dosage not specified. His tuberculosis was considered arrested during his stay at the state hospital but there is no record of X-rays or sputum examinations during this period. On September 24, 1930, discharged from state hospital and admitted to Veterans Administration Facility, North Chicago, Illinois, where a

diagnosis of general paresis was continued, and spinal-fluid Wassermann was 100 per cent positive, and colloidal gold curve was 3334433300. Blood Kahn and Wassermann positive. Clinical symptoms and neurological findings typical for general paresis; while on admission the pulmonary tuberculosis was considered to be active but no evidence of activity could be obtained subsequently. X-ray showed involvement of right upper lobe with considerable fibrosis and calcification. Sputum examinations unobtainable because of mental condition. Antisyphilitic treatment begun in November, 1930, when he was given a course of tryparsamide and mercury. On January 4, 1932, to April 25, 1932, given 12 injections of mercury and from January 7, 1932, to March 31, 1932, nine injections of tryparsamide. From April 7, 1932, to May 16, 1932, given 7 injections of bismarsen, following which patient developed a stomatitis and the treatment was discontinued. Treatment was again instituted in June, 1934, and 10 injections of sodium-bismuth-tartrate and 2 of iodobismithol were given. In February and March, 1935, he had 5 injections of tryparsamide. *Present status:* Tuberculosis apparently arrested. Patient well nourished; however, he is out of contact, is deaf, has frequent "involuntaries," becomes excited and has had an occasional seizure.

Summary: Patient with pulmonary tuberculosis becomes infected with syphilis; the tuberculosis apparently becomes arrested and remains so, although paresis developed in 1929 and the patient received vigorous antisyphilitic treatment, including diathermy. Fifteen years after onset of tuberculosis and six years after onset of paresis, the patient is in good condition.

2: H. K., white, male, aged 41, admitted May 19, 1926; still in hospital September 15, 1935. History of chancre in 1918. Symptoms of paresis began in April, 1923; and patient admitted to a state hospital in October, 1923, where diagnosis of general paresis was made, based on typical symptoms, neurological findings and a four-plus blood and spinal-fluid Wassermann. Although emaciated, chest reported negative. No record of antisyphilitic treatment at the state institution, and on May 19, 1926, discharged as improved: had gained 18 lbs. On admission to Veterans Administration Facility, North Chicago, Illinois, in addition to general paresis, patient found to have far-advanced pulmonary tuberculosis with cavitation involving right upper lobe. Diagnosis confirmed by X-ray and positive sputum tests. On admission, blood Wassermann was negative. Spinal Wassermann was 100 per cent positive; colloidal gold 5555542100. On January 14, 1932, antisyphilitic treatment was instituted, and 25 injections of tryparsamide given until July 28, 1932. From August 4, 1934, to October 4, 1934, received 10 injections of bismuth, and from April 4, 1935, to May 27, 1935, eight injec-

tions of tryparsamide. On August 9, 1932, spinal fluid, Kahn, and Wassermann were negative, and the gold curve 1112111000. On July 16, 1935, spinal-fluid Wassermann negative and gold curve 1122110000. *Present status:* Patient a deteriorated paretic, remaining afebrile with but occasional small rise in temperature and nutrition good. Recent sputum examinations negative. X-ray still reveals cavitation in right upper lobe, cavity perhaps being somewhat smaller than on admission.

Summary: Three years after the onset of patient's paresis, far-advanced pulmonary tuberculosis was discovered. Twelve years after onset of paresis and nine years after far-advanced tuberculosis was present, patient is alive and in fairly good general condition.

3: B. H., white, male, aged 39, admitted to Veterans Administration Facility, North Chicago, Illinois, October 1, 1930, and transferred to another Veterans hospital, June 20, 1935. History of chancre in 1925: treated by 15 "shots." Apparently mental symptoms appeared early in 1929, and at same time symptoms of pulmonary disease, so that patient sought treatment because of pulmonary complaints. On July 3, 1929, hospitalized by Veterans Bureau, and diagnosis of general paresis based upon positive serological and neurological findings, and also pulmonary tuberculosis, active moderately advanced-B made, based on X-ray, physical examination and clinical observation. Intensive antisyphilitic treatment 3 gm. doses of tryparsamide and $\frac{1}{8}$ gr. doses of mercury-oxycyanide weekly given. However, spinal Wassermann still 100 per cent positive and gold curve 5555432100. X-ray and physical examination indicated that pulmonary condition was not progressing and sputum was negative; and, January 13, 1930, patient transferred to another hospital (Veterans) where the blood Kahn and Wassermann were found positive. Chest however was considered negative, and sputum examination was negative and another course of antisyphilitic treatment of tryparsamide and bismuth was administered. On October 6, 1930 admitted to Veterans Administration Facility, North Chicago, Illinois. Blood, Kahn and Wassermann negative; spinal-fluid Wassermann 100 per cent positive; gold curve 3443310000. X-ray showed evidence of tuberculosis of right upper lobe. Three sputum examinations positive for tubercle bacilli in October, 1930; so that diagnosis of general paresis and chronic pulmonary tuberculosis, active moderately advanced-B, was again made. Another course of antisyphilitic treatment of tryparsamide and bismuth was administered. On December 14, 1933, a cholecystectomy was done under ether anaesthesia because of acute gall-bladder disease. *Present status:* Pulmonary tuberculosis became quiescent, sputum examinations were negative, X-ray showed evidence of fibrosis and calcifications of the pulmonary lesion, mental condition was much improved, patient well nourished. Serological examination, spinal-

fluid Wassermann was 50 per cent positive on April 20, 1935, and gold curve was 0232111000. On June 20, 1935, transferred to another hospital in order to be closer to home.

Summary: Four years after history of chancre patient developed mental symptoms and at about same time symptoms of pulmonary disease. Received intensive antisyphilitic treatment at various hospitals, developed intercurrent gall-bladder disease, and made slow but satisfactory recovery after cholecystectomy. Pulmonary tuberculosis becomes quiescent and mental condition improves. Serological findings improve; and six years after onset of paresis and pulmonary tuberculosis, the tuberculosis is apparently quiescent and mental condition is very good.

4: W. E., white, male, aged 41, admitted to the Veterans Administration Facility, North Chicago, Illinois, November 7, 1930: died January 23, 1933. History of chancre in 1916, followed by positive Wassermann. Received 11 injections of mercury and neoarsphenamin. In fall of 1923, told he had pulmonary tuberculosis. In 1924 developed nervousness, weakness and twitching of the right arm. In 1925, he was first hospitalized for tuberculosis; and on October 18, 1925, entered a Veterans Hospital, where he was found to have pulmonary tuberculosis and general paresis. Sputum examinations positive for tubercule bacilli on November 14, 1925, and January 14, 1926. Blood Wassermann 100 per cent positive. Spinal-fluid Wassermann moderately positive; gold curve 5544320000. X-ray showed evidence of involvement of both lungs, chiefly left. Remained at this hospital from October 18, 1925, to June 3, 1930, receiving intensive antisyphilitic treatment consisting of neosalvarsan, bismuth and mercury, without clinical improvement. Tuberculosis, however, considered quiescent at time of discharge. On November 7, 1930, admitted to the Facility at North Chicago, where in addition to general paresis there was noted a right hemiplegia, with partial paralysis of right arm and leg (syphilitic). Pulmonary tuberculosis at this time considered quiescent. On November 11, 1930, blood Wassermann 50 per cent positive and blood Kahn four-plus. On Nov. 18, 1930, spinal-fluid Wassermann 100 per cent positive: gold test 0012110000. On March 17, 1931, spinal Wassermann was 75 per cent positive and gold curve 2233321000. Both Wassermann and Kahn were negative on May 12, 1931. Seven sputum examinations were negative in November, 1930. X-ray reported fibrosis, probably due to quiescent tuberculosis. Antisyphilitic treatment was instituted December 4, 1930, and received 27 injections of tryparsamide, gm. 1½, and 9 injections of 3 gm. each. Also received 3 injections of mercury. Last injection of mercury given October 21, 1931. On October 21, 1931, patient had haemoptysis of 4 ounces, and antisyphilitic treatment was discontinued. However, patient improved; and on January 7, 1932, tryparsamide therapy was resumed and patient

received 7 injections of tryparsamide, the last on May 26, 1932. In July, 1932, haemoptysis again, and from this time on patient continued to show haemoptysis from time to time until death. Ran low-grade fever, and, for three months preceding death, was confused and at times stuporous. On December 31, 1931, X-ray report showed involvement of the left lung, probably active.

Summary: Nine years after symptoms of paresis began and ten years after onset of tuberculosis, patient died apparently of paresis, the tuberculosis, however, being an important contributory cause. It will be noted that the pulmonary tuberculosis was considered quiescent on admission; following the use of tryparsamide, his pulmonary condition became activated.

5: C. M., white, male, aged 30, admitted January 6, 1931: died January 30, 1931. Primary syphilitic lesion in 1918 while in service, said to have been treated at that time. No record as to type or amount of treatment. At this time also, patient stated he was told by physicians that he had a "spot" in the left lung, size of dime. Since 1925, he had been suffering from pleurisy and bronchitis, and in April, 1928, these conditions had become worse and haemoptysis occurred. In July, 1928, sputum was found positive for tubercle bacilli. On December 12, 1928, was first hospitalized by Veterans Bureau and diagnosis of general paresis and chronic pulmonary tuberculosis active made. Left hospital on December 24, 1928, against medical advice. Again hospitalized by the Veterans Bureau on February 14, 1929, after short period in local county hospital, and remained under care of the Veterans Administration until death on January 30, 1931. On January 6, 1931, he was admitted to the facility at North Chicago, Illinois, where diagnosis of chronic pulmonary tuberculosis, active far-advanced-C, with spontaneous pneumothorax on the left, partial, and general paresis, was made. These diagnoses confirmed by positive physical and X-ray findings, positive sputum, blood and spinal Wassermann; Kahn was three-plus; and gold curve 3445543210. Neuropsychiatric examination was considered characteristic of a deteriorated paretic. No record of antisyphilitic treatment prior to admission to this hospital except patient's statement concerning initial treatment. At North Chicago, he was given three weekly injections of 3 gm. tryparsamide, the last on January 22, 1931. On January 28, 1931, had a mild seizure, from which apparently recovered. On January 29, 1931, had another seizure, collapsed, went into a coma, and died on January 30, 1931. Postmortem examination gave evidence of bilateral pulmonary tuberculosis with cavitation, tuberculous ulcer of the ileum, syphilitic aortitis, chronic degenerative myocarditis, chronic parenchymatous nephritis.

Summary: Seven years after the onset of the primary syphilitic lesion patient develops symptoms of tuberculosis. Does not seek treatment until

three years later when found to have paresis as well. Dies two years following initial hospitalization for tuberculosis or about twelve and a half years after the onset of syphilis, six years after onset of his tuberculosis, death following two paretic seizures although the tuberculosis in itself was undoubtedly sufficient to account for his death.

6: E. D., white, male, aged 40, admitted March 28, 1927, died January 4, 1928. Primary lesion in 1905 or 1906, symptoms of paresis February, 1922. Admitted to state hospital on March 20, 1922, where blood Wassermann 3-plus; spinal-fluid Wassermann 4-plus; gold curve 5555555321: which, together with characteristic neurological findings, led to diagnosis of general paresis, April 5, 1922. Received intensive treatment of 15 injections of neosalvarsan, 17 injections of mercury, 20 of sulpharsphenamin, 22 of tryparsamide, and 10 of gray oil of mercury (dosage not stated). In July, 1925, tuberculosis was suspected, but sputum was negative. In March, 1926, was inoculated with malaria and had fifteen chills. On March 28, 1927, transferred to Veterans Administration Facility, North Chicago, Illinois. Here blood Wassermann negative on April 8, 1927, and November 1, 1927. Spinal-fluid Wassermann 75 per cent positive on April 26, 1927, and 25 per cent positive on December 16, 1927. Gold curve 2334420000 on April 16, 1927 and 1232310000 on December 16, 1927. X-ray of April 20, 1927, reported evidence of pulmonary tuberculosis but, in conjunction with clinical findings, lesion was considered inactive. Further antisyphilitic treatment was recommended for patient, who had deteriorated markedly. From July 21, 1927, to November 17, 1927, given 18 weekly injections of tryparsamide, 3 gms. each, 17 weekly injections of 1/10 gm. each of mercury salicylate. On December 9, 1927, developed cough, haemoptysis, and fever, and became progressively worse. X-ray and physical examination revealed diffuse bronchopneumonic involvement and tubercle bacilli found in sputum. Died, January 4, 1928. Postmortem examination revealed extensive bronchopneumonic tuberculosis, with small cavities, anthracosis, and fatty liver.

Summary: Patient who received initial syphilitic infection in 1905, developed symptoms of paresis in 1922, received intensive antisyphilitic treatment including malaria from 1922 to 1927. Tuberculosis was first considered in July, 1925, but activity was not found. In April, 1927, there is X-ray evidence of tuberculosis but the clinical findings indicate no activity. Finally, after another protracted course of tryparsamide and mercury, patient develops fulminating bronchopneumonia which rapidly kills him. Death occurs six years after the onset of his paresis and twenty-two months after onset of tuberculosis.

7: T. Y., white, male, aged 32, admitted October 25, 1928; died April 20, 1929. No definite history of primary lesion, but penile scar reported in 1918.

On March 5, 1919, blood Wassermann was four-plus, and neosalvarsan, mercury and potassium iodide were administered. Mental symptoms were said to have been noted at this time, as well as Argyle-Robertson pupils. However mental symptoms apparently became prominent in 1925, and, after period of treatment in private sanatorium, on January 7, 1926 committed to a state hospital, where diagnosis of general paresis made on January 21, 1926, supported by characteristic symptoms, neurological findings and four-plus spinal-fluid Wassermann. The blood Wassermann was negative. There is no record of antisyphilitic treatment during stay at this institution and no record of pulmonary tuberculosis. On October 25, 1928, patient was admitted to the Veterans Facility, North Chicago, Illinois, where, in addition to general paresis, far advanced pulmonary tuberculosis found, as shown by X-ray. Patient was greatly deteriorated and unable to coöperate for satisfactory chest examination. Blood Wassermann negative. Spinal fluid Wassermann 50 per cent positive and gold curve 0000000000. Patient untidy and went progressively downhill, ran low-grade fever, and died April 20, 1929. There was no antisyphilitic treatment administered, because of advanced pulmonary disease and poor general condition. Postmortem revealed tuberculosis of both lungs, syphilitic aortitis, myocarditis, suppurative nephritis, acute congestive hepatitis and gastroenteritis.

Summary: Patient, who had definite evidence of syphilis in 1919, develops paresis in 1926. Far-advanced pulmonary tuberculosis is discovered in October, 1928, and death occurs on April 20, 1929, three years after diagnosis of paresis, seven months after discovery of tuberculosis.

8: T. P. N., white, male, aged 32, admitted June 3, 1930; died November 3, 1930. History of gonorrhoea in 1922. On March 19, 1923, was discharged from the army because of epilepsy which had been considered at one time of hysteroid type. While in service in 1922 had tertian malaria. On April 11, 1923, blood Wassermann was negative and March 1, 1924, diagnosis of primary genital syphilis was made. On April 11, 1924, hospitalized in Veterans Hospital, and diagnosis of general paresis was made confirmed by positive blood and spinal-fluid Wassermann and gold curve of 4553210000. Intensive antisyphilitic treatment of neoarsphenamin, tryparsamide, mercury and potassium iodide administered. Patient's mental condition improved. Serological examinations practically negative and on May 11, 1925, patient discharged as having received maximum benefit. Blood Wassermanns were negative in 1926 and 1928, and on January 24, 1928, patient convicted of manslaughter and, while serving sentence, he developed pulmonary haemorrhages. On March 3, 1929, sputum positive for tubercle bacilli, and patient accordingly sent to the hospital for criminally insane. Paroled on March 4, 1930. On June 3, 1930, admitted to North Chicago, Illinois, where, in addition to

general paresis, found to have far-advanced pulmonary tuberculosis with cavitation, confirmed by physical and X-ray examination with positive sputum; blood and spinal-fluid examinations and Kahn negative; gold curve 0112221000. No antisyphilitic treatment given during stay here. Course progressively downward. Mentally he remained in good contact and revealed no prominent symptoms. Died on November 7, 1930.

Summary: Patient develops pulmonary tuberculosis while in prison and dies of this condition two years after it is discovered, six and one-half years after onset of paresis.

9: E. Mc., white, male, aged 38, admitted January 30, 1931, remains in hospital on September 15, 1935. No history of primary or secondary lesion. In fact, very little definite chronological information prior to admission. However, seems to have developed mental symptoms and some type of epileptiform seizures which led to his being placed in a county asylum late in 1930. Admitted to the Veterans Administration Facility, North Chicago, Illinois, January 30, 1931. Blood-Wassermann examinations negative on March 25, 26, 27, 28 and 31, 1931. Blood Kahn 3-plus, March 25, 1931, and 4-plus on March 27, 28 and 31, 1931. Spinal-fluid Wassermann negative March 10, 1931; 75 per cent positive, March 31, 1931. Gold curve 1122211000, March 10, 1931, and 1122210000, March 31, 1931. Under observation for considerable period of time before diagnosis of paresis made. The epileptiform seizures which he has almost daily have been a prominent factor. Serological findings were not typical of paresis, but his symptoms (such as ideas of grandeur), and neurological and clinical findings were considered as establishing diagnosis of general paresis. No record of previous antisyphilitic treatment, and no previous record of pulmonary tuberculosis. Antisyphilitic treatments instituted: from November 2, 1931, to September 1, 1931, given 34 injections, 1/10 gm. each, of mercury salicylate, 35 injections of tryparsamide, 3 gm. each. Developed fever, haemoptysis and cough on September 1, 1932, and on September 7, 1932 sputum examinations were positive for tubercle bacilli. Antisyphilitic treatment discontinued, and patient placed on bed-rest. Fever subsided, and general condition improved, so that antisyphilitic treatment again started with tryparsamide: from February 2, 1933, to April 27, 1933, thirteen injections of 3 gm. each were made. On May 11, 1933, sputum examination again positive. September 11, 1933, haemoptysis occurred again. However, following this, pulmonary condition improved, became quiescent, and temperature became normal, so that from July to December, 1934, given course of bismuth. In January and February, 1935, was also given tryparsamide and bismuth, and in August of 1935, again given bismuth and tryparsamide. Has also been receiving luminal. *Present status:* Epileptiform seizures continue practically daily: are momentary, accompanied by a cry,

followed by loss of consciousness and involuntary urination and a short period of confusion. Pulmonary tuberculosis quiescent; X-ray shows a regression of the lesion, with evidence of fibrosis. No cough or expectoration. Mentally, patient remains out of contact and shows very little change.

Summary: A paretic without typical serological findings, whose outstanding symptoms are frequent seizures and deterioration, following intensive antisyphilitic treatment develops pulmonary tuberculosis, which becomes quiescent under general hygienic management, paresis apparently remaining stationary.

10: M. B., white, male, aged 40, admitted September 24, 1930. In 1922 developed manifestations of secondary syphilis, including positive Wassermann. In June, 1923, developed speech defect and right facial paralysis. Blood and spinal Wassermanns negative. Treated intensively and several Swift-Ellis treatments were given, following which he became irrational, developed paralysis of legs, bowels and bladder with some anaesthesia of the legs. Then hospitalized at a county hospital and given 6 intravenous neosalvarsan injections followed by spinal drainage. On August 8, 1924, hospitalized by the Veterans Bureau. All serological examinations negative. Patient considered to have at this time cerebrospinal syphilis, with psychosis. October 6, 1924, admitted to state hospital where blood and spinal-fluid Wassermanns were negative on January 16, 1926. During stay at state hospital, showed deterioration, and the diagnosis lay between cerebrospinal syphilis and paresis, the former being favored. No record of pulmonary tuberculosis at this time. On September 24, 1930, admitted to Veterans Facility, North Chicago, Illinois. Serological examinations at this Facility showed blood Wassermann and Kahn negative, September 30, 1930. Spinal fluid Wassermann 50 per cent positive, October 14, 1930. Gold curve 0111110000. Subsequent spinal-fluid examinations, March 17, 1931 and September 22, 1931, were negative, and the gold curve the same type as previously mentioned. Although in this case, as in the preceding, serological findings were not typical of paresis, yet this was probably due to the treatment. After period of observation based on symptoms and neurological findings, diagnosis of general paresis was made. In addition, the patient had spastic paraplegia, incomplete, of lower extremities with bladder paralysis. X-ray examination showed evidence of old tuberculous lesion with calcification. Antisyphilitic treatment was instituted, and from December 4, 1930, to March 31, 1932, received 52 injections of mercury, gm. 1/10 each, and 54 injections of tryparsamide, gm. 3 each, with several rest-periods between. In April, 1932, received potassium iodide, gr. 30 for 26 days. From May to July, 1932, received 11 more injections of tryparsamide and 12 of mercury, and in April, 1935, received several injections of tryparsamide again. Has shown considerable mental deterioration. How-

ever, able to walk slowly when holding on to something. In September, 1933, following paroxysm of coughing, haemorrhage occurred, but there has been no other evidence of active tuberculosis. Several subsequent X-rays of the chest reveal old calcified lesions in both upper lobes. Temperature has remained normal with just an occasional rise. *Present status:* Mentally, patient is entirely out of contact. Pressure sores, which he is frequently subject to because of his paralysis, are entirely healed. The tuberculous lesions are apparently arrested.

Summary: Case of paresis with atypical serological findings and spastic paraplegia of lower extremities, receiving intensive antisyphilitic treatment. Has X-ray evidence of old tuberculosis and, except for one recorded period of haemoptysis, this lesion is apparently unaffected by his paresis.

11: K. E., male, white, aged 43, admitted July 10, 1935, transferred August 7, 1935. No history of primary or secondary lesion. Patient stated he had been treated for rectal fistula several years after discharge from service (which occurred in 1919). In February, 1932, developed symptoms of pulmonary tuberculosis, was treated first at private sanitarium; then on June 6, 1932, admitted to Naval Hospital, where, in addition to pulmonary tuberculosis confirmed by positive sputum and physical examinations, blood Kahn was found to be 4-plus on June 7, 1932, and July 14, 1932. On December 21, 1932, spinal fluid was 4-plus and gold curve 4402312000, which together with mental and neurological findings established diagnosis of general paresis. Discharged April 18, 1933. From September 9, 1934, to May 1, 1935, given routine treatment for tuberculosis at Veterans Hospital. On July 10, 1935, admitted to Veterans Administration Facility, North Chicago, Illinois. Blood Wassermann negative, spinal fluid Wassermann 100 per cent positive and gold curve 4555432100. In addition to general paresis, found to have active far-advanced-A pulmonary tuberculosis with cavitation confirmed by X-ray, physical examination and positive sputum. No record of antisyphilitic treatment although it was apparently recommended during his stay at Naval Hospital. On August 7, 1935, transferred to another hospital closer to his home.

Summary: A paretic with far-advanced pulmonary tuberculosis, with but slight activity of his tuberculosis. Gave history of preceding rectal fistula (which is often found in tuberculosis), pulmonary symptoms becoming prominent late in 1931 and diagnosis of paresis made in December, 1932. Patient at present being in good mental contact, but showing far-advanced tuberculosis with slight activity.

Since writing this paper a twelfth case has been admitted to this Facility, which fits in with this series and, although time does not permit a de-

tailed account of this case, it is of interest to mention just briefly. Patient white male, aged 41, admitted September 13, 1935, with history of syphilis having been found in 1929 and diagnosis of general paresis made in December 1932. On admission to North Chicago, spinal-fluid Wassermann was 100 per cent positive, gold curve 5555543210, and neurological findings in keeping with diagnosis of general paresis. In addition, X-ray examination revealed fibroid tuberculosis involving both upper lobes, and sputum examination positive for tubercle bacilli. Physical findings practically negative. No history of pulmonary tuberculosis having previously been found. Thus, this is another case of paresis that developed tuberculosis, and, although hospitalized at several institutions, there is no record of pulmonary tuberculosis until routine chest X-ray was taken which led to sputum examination. Patient's general condition appeared good upon admission.

CONCLUSIONS

To draw general conclusions from such a small series would appear presumptuous. Perhaps more questions are raised than answered by this analysis; however, the writer feels warranted in pointing out certain trends and in emphasizing the difficulty inherent in any effort to evaluate the interrelationship of these two conditions and perhaps in suggesting the lines along which further study might be of value.

1. Pulmonary tuberculosis, while not very common in paretics, occurs sufficiently often to warrant careful observation for this condition. The diagnosis of pulmonary tuberculosis in otherwise normal individuals is frequently not made until the lesion is far advanced, not necessarily because of failure to make a thorough physical examination but (as has been found by Lawrason Brown and others) because of atypical and absent physical signs even in the presence of good-sized cavities. In paretics, especially the deteriorated, who develop pulmonary tuberculosis, the diagnosis is frequently made even more difficult by the patient's inability to coöperate. Recourse must therefore be made to all available diagnostic means, particularly the X-ray, since sputum is often unobtainable.

2. The problem of pulmonary tuberculosis in paresis is of importance, not only from the standpoint of the individual patient whose therapy will necessarily be modified by the type, extent and activity of pulmonary lesion, but also from the possibility of the spread of tuberculosis

to others, particularly in institutions. Obviously, any form of fever therapy is contraindicated in the presence of active tuberculosis.

3. In most of the cases in this series the syphilitic infection preceded the tuberculosis, which is in accord with the findings of many observers; the significance of this, however, still remains an open question. That tuberculosis occurs in deteriorated paretics is no indication of a specific predilection of paretics for tuberculosis, because tuberculosis occurs not infrequently in deteriorated praecoxes as well (in fact, more frequently according to McGhie and Brink).

4. When tuberculosis occurs in a paretic, the course is not necessarily more severe than in a nonparetic; it may be milder, it may pursue its usual course but it also may be more severe. At times when it is more severe it is difficult to determine whether perhaps the antisyphilitic treatment itself was a factor in aggravating the condition.

5. Pulmonary haemorrhages have occurred following the use of tryparsamide and tryparsamide and mercury, and in at least one instance a case of quiescent tuberculosis was apparently converted into a fulminating tuberculous bronchopneumonia following such treatment. To be sure, haemorrhages occur frequently in pulmonary tuberculosis without any complicating syphilis and without antisyphilitic treatment. It seems (even from this small series) that tryparsamide, when administered, should be given in smaller doses and shorter courses, with more frequent rest-periods, particularly when there is a history of pulmonary haemorrhage.

6. When paresis occurs in a tuberculous individual with an old healed lesion it may have no effect on that lesion, even though vigorous antisyphilitic treatment, including fever therapy, is given. Therefore, in a well-healed lesion with calcification and fibrosis, diathermy and perhaps even malarial therapy may be attempted, but the patient should be watched even more closely than usual.

7. Paretics live much longer at present than formerly. Whether this will lead to a change in incidence of tuberculosis in the paretics remains to be seen.

8. Inasmuch as paretics do live for considerable periods, even in the presence of pulmonary tuberculosis, it would seem that, when the mental condition of the patient permits, the usual indication for such collapse therapy as pneumothorax and phrenicoexairesis could be employed with benefit.

In conclusion it would be interesting and perhaps valuable to compare

groups of paretics with tuberculosis with groups of similar tuberculosis without paresis on the one hand and with groups of similar paretics without tuberculosis on the other hand.

The writer wishes to express his appreciation to the hospital authorities for placing this material at his disposal and particularly wishes to thank the Librarian, Miss Esther Peterson, and the Social Service Worker, Miss Rose Schlichter, for their invaluable assistance.

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THE FEASIBILITY OF ARTIFICIAL PNEUMOTHORAX IN MINIMAL CASES OF TUBERCULOSIS[1,2]

GEORGE C. TURNER AND LOREN L. COLLINS

Phthisiologists are agreed that the chances for recovery from pulmonary tuberculosis are greatly increased by early diagnosis. The extensive campaigns and surveys made among various groups of people, particularly high-school, university students and hospital nursing staffs, have uncovered many new minimal cases of tuberculosis. Many of these cases are of a much earlier type than we have been accustomed to dealing with in the past.

A perusal of the literature and interviews with various authorities in the field bring to light a singular lack of unanimity in the treatment recommended for these cases when they are discovered. Many authorities still recommend rest alone for the treatment of minimal cases. Surgeons have recently recommended some form of collapse therapy. O'Brien (1) states very definitely that many minimal cases spread to far-advanced lesions, because they are treated by rest alone. He believes that collapse therapy should be instituted at once. Phrenicoexairesis is, in his opinion, the most feasible form and should be tried first in most cases.

Alexander (2) states "that in experienced hands, paralysis of the phrenic nerve is a far simpler and less dangerous procedure than pneumothorax, and has the additional advantage that a prolonged period of refills is not necessary." He states further that "there are exceptions to this rule, and that individual cases must be studied carefully before determining which procedure holds the best prospects for success in the case under consideration." Head (3) takes a more definite stand and states that "in his opinion, minimal tuberculosis should not require a prolonged disability." In cases in which the prognosis demands a strict rest regimen of more than a few months, he believes that collapse therapy should be instituted and the patient allowed to continue the physical

[1] From the Admission Ward of the Chicago Municipal Tuberculosis Sanitarium, Chicago, Illinois.

[2] Presented in part before the Clinical Section of the 31st annual meeting of the National Tuberculosis Association, Saranac Lake, New York, June 26, 1935.

activity entailed in light occupations. He believes that pneumothorax is the procedure of choice and states, that "in his opinion a phrenic operation would demand a more prolonged rest regime."

Davison (4) working in our own clinic states that "experience has shown that many minimal cases slowly or rapidly progress under rest treatment alone, and that pneumothorax is practically free from hazard in these cases." He believes that nearly all minimal lesions should be collapsed, when possible, with pneumothorax. If pneumothorax fails, a temporary phrenic operation should be performed. There are many authorities who have advocated the use of pneumothorax in some specially selected minimal cases. A study of the cases reported by the "infiltrate school," Lassen (5), von Romberg (6), Dorendorf (7) and Katz (8), shows that they all believe in waiting until there is evidence of excavation or a positive sputum. Gähwyler (9) is the only one of this school who believes in immediate induction of pneumothorax. On the whole his results are much better than those of the more conservative German authors of the "infiltrate school."

Lawrason Brown (10) has predicted that pneumothorax would be used in all early cases in the future. Burrell (11) in England has sounded a similar note. Cedric Shaw (12) reported excellent results in 43 minimal cases treated by pneumothorax. By comparison with his moderate and far-advanced groups the results were very satisfactory. He advocated the increased use of pneumothorax in this group. Myers has been a strong advocate of pneumothorax in minimal cases for a number of years, and Myers and Levine (13) have recently reviewed the literature on this subject and reported very favorable results in 52 cases so treated. Myers concludes that all minimal cases which show any signs of "progression" should be treated by pneumothorax immediately.

Because of these varied opinions and to determine our own future course in these cases, we have made an analytical study of all minimal cases admitted to the Chicago Municipal Tuberculosis Sanitarium, from the years 1930 to 1935. In selecting these cases, we have excluded all but the minimal cases conforming to the five diagnostic points formulated by Lawrason Brown (14) and to the standards set by the National Tuberculosis Association for minimal cases (1931 revision). These requirements forced out of consideration many cases in which the diagnosis could not be proved and many others which were on the borderline between the minimal and moderately advanced groups.

By this method we selected 139 minimal cases for study They

were grouped as follows: 50 cases were recommended for pneumothorax; 65 cases were treated by rest alone, and 24 cases were treated by phrenicoexairesis alone. (The major portion of this paper is devoted to the study of the 50 minimal cases recommended for pneumothorax.)

Women predominated in the pneumothorax series, there being 38 women and 12 men. The youngest was 14 years and the oldest 48 years. The majority, that is, 33, were from 18 to 25 years of age. Of the whole group, 27 were office-workers, 5 were nurses, 12 were housewives, 4 high-school students, and 2 were in heavy occupations. Of the fifty, 29 had been ill less than 6 months. The sputum was found positive in 31, and negative in 19.

The symptoms were not marked in any of these cases, but there were 30 cases which had some cough and 33 had a moderate amount of expectoration; 19 cases showed haemoptysis of 1 dram or more previous to admission; 17 of the cases had a history of pleurisy and 31 of the cases had lost from 10 to 15 lbs.; 20 cases showed a temperature of 99° or slightly higher when they came under our care. Physical findings were negligible in the majority of these cases. There were only 11 cases in which râles were found in the chest, while 29 showed some impairment of resonance. X-rays showed that 15 cases had shadows commonly called "infiltrates." The average extent of involvement, as estimated by careful examination of stereo-roentgenogram, was 8 per cent of one lobe.

Of the 50 cases recommended for pneumothorax, 5 cases refused and in 5 cases pneumothorax was attempted but no free space was found. These cases were then treated by rest alone and constitute our first control group. Of the 45 pneumothoraces attempted, a free space was obtained in 40, or 88 per cent. This is somewhat higher than the average for pneumothorax in more advanced lesions, as reported by our own and other clinics.

When we consider the percentage in which an effective collapse was obtained, we find a much more striking figure. There were 4 cases in which small adhesions were present, but there was no case in the group of 40 cases receiving pneumothorax in which the diseased area was not collapsed by the pneumothorax obtained. This gave 100 per cent of effective collapses in this group of 40 cases in which a free space was found.

The complications have been remarkably low. Of the 40 cases receiving pneumothorax, we have had but one case of pleural effusion.

This case stopped receiving pneumothorax at the end of 8 months, achieved a good end-result, and has been working for more than one year. We had one case of obliterative pleuritis, which forced the termination of pneumothorax at the end of 9 months. However, this duration was long enough to achieve a "clinical result," and the patient is well and has been working for 18 months. We have yet to see a minimal pneumothorax case show progression of the disease in the treated lung, or metastasize to a new lobe or exhibit an exacerbation of a previously existing lesion in the contralateral lung. There have been no extrapulmonary complications up to the present time.

We have made a study of the sputum results in these 40 cases, and found that 15 were always negative, and 25 positive. Of the 25 positive cases, 8 were changed previous to pneumothorax induction, leaving 17 cases positive at the time pneumothorax was instituted.

Inasmuch as the conversion time of the sputum is considered important, the conversion time was carefully worked out in these cases. We find that in the 8 cases which were converted before pneumothorax was instituted, 6 were converted in 1 to 3 months, one in 6 months and one in 8 months, giving us an average conversion time of 3.5 months for these 8 cases. A similar study of the 17 cases which were positive at the time that pneumothorax was induced reveals that 8 cases were converted in 1 month, 3 cases in 2 to 3 months, 2 cases in 4 to 6 months, 2 cases in 7 to 12 months, giving an average conversion time of 4.6 months and percentage of conversion of 100 for the entire group of positive cases.

You will note that in the last 4 cases the conversion time was much longer than it was in the other 21 cases.

We will digress here to state that various men, including Myers and Levine (13), Lassen (5), von Romberg (6), Cardis (15), and Peters (16) have advised a period of "watchful waiting" before the induction of pneumothorax. In the 40 cases described, this period of study was 2 months or less in the majority of cases. There were 5 cases in which the period of waiting was from 4 to 8 months. When we consider the results of watchful waiting in this group in which we waited for definite evidence of progression, we wonder as to the advisability of this expectant policy. Of these 5 cases, one case was converted before the pneumothorax was instituted. One case was converted in 9 months, one in 10 months, one in 18 months and one in 20 months, giving us an average conversion time for the 4 cases of 14.2 months.

We stated that the average conversion time for 17 cases positive when pneumothorax was instituted was 4.6 months. If we subtract the above mentioned 4 cases in which we delayed, we get a conversion time for the remaining 13 cases of 1.6 months. In other words a minimal case which is positive at the time of pneumothorax induction, will usually change in less than 2 months if pneumothorax is done at once. If we delay, conversion may not be so prompt. The importance of this consideration is obvious. Roloff (17) showed from a study of 1,128 cases of pneumothorax of all types, followed for a period of one to twelve years, that the results were much better in the cases in which pneumothorax had been induced within three months after a positive sputum was first obtained.

Summing up the study of the conversion time we find that of the 25 positive cases, 25, or 100 per cent, converted before or after pneumothorax treatment. The average conversion time for the whole group is 4 months.

Even short periods of observation may be dangerous, as shown in the case of

E. E., female, aged 24, a stenographer, ill 2 months previous to admission, with low-grade fever, positive sputum, and X-ray findings of a cloudy infiltrate in the left midlung field. Her lesion seemed so small and symptoms so slight that pneumothorax was delayed. She was placed on absolute bedrest for one month. During this time, she showed no clinical evidence of activity, but an X-ray taken at the end of the month showed that the "infiltrate" had excavated and presumably the detritus blocked one of the main bronchi in the left lower lobe. Moreover there was a diffuse extension of the diseased process throughout the whole left lower lobe. Further delay being obviously out of the question, pneumothorax was induced and it controlled this lesion within 4 months. This patient is now well and working.

A study was made of the hospital stay after pneumothorax, the total hospital stay and the total disability of the patient up to the time of discharge. The period of total disability was taken to be the total time the patient was unable to work at his or her original occupation.

In table 1 we see again that the group in which induction of pneumothorax was delayed have a longer hospital stay and a much longer period of total disability. In fact, if the 5 delayed cases were subtracted from the 17 cases positive at pneumothorax induction, the hospital stay and total disability time of the positive cases would very

nearly approach the more favorable hospital stay of the negative and previously converted groups.

The hospital stay is longer here than in many other sanatoria for this type of lesion because most of our patients have to return directly to their former occupation on discharge. For purposes of this study, the hospital stay makes a good control, because it very nearly coincides with that of the groups that received rest alone. We believe that in the future the hospital stay may be greatly reduced and many of these cases may be sent back to work at a much earlier date than we formerly considered safe. As we are more certain of our results, we may con-

TABLE 1

Hospital stay and disability time

40 discharged cases of pneumothorax

	40 CASES	15 CASES ALWAYS NEGATIVE	8 CONVERTED BEFORE PNEUMOTHORAX	17 POSITIVE AT TIME OF PNEUMOTHORAX	5 CASES DELAYED
				months	*months*
Hospital stay after pneumothorax	6.3 months	5.2 months	4.5 months	8.7	12
Total hospital stay	8.1 months	5.9 months	7 months	11.8	17
Total disability at time of discharge	11.9 months	9.9 months	10.5 months	14.3	20
Total disability	14.6 months	14 months	15* months	16.7	27.25
Still disabled	1 case	—	1 case†	—	—
Well and able to work, but unemployed	2 cases	2 cases	—	—	—

* One case ill 2½ years previous to treatment.

† Diabetic (controlled).

sider it feasible to allow these people to return to work long before their course of pneumothorax treatment has been completed. This plan would be in line with the ambulatory treatment as advised by Myers (18), Tice (19), Hruby (20), Poix and Bosnières (21), and others. Our own recent experience agrees with Poix and Bosnières in that those cases which received at least 6 months' rest treatment after pneumothorax was induced did better than those in which this was not possible.

Studying the present status of these 40 pneumothorax cases, we find that 11 have reëxpanded and are well and working, and 29 are still under treatment. Of these 29 cases under treatment, 26 are well and working, one is a diabetic (controlled) or well, but not working, two cases are

well but unemployed. Summing up the present status of the whole group, we find that 37 of the 40 cases are well and working, and 3 cases are well but not working.

In the 11 cases that reëxpanded, we find that 3 cases received pneumothorax from 3 to 8 months, 6 cases for 9 to 15 months, and 2 for 18 to 20 months. One case has been reëxpanded for a period of three years; 7 for from 1 to 2 years; and 3 cases have been reëxpanded for a period of less than a year. All 11 cases are working and are symptom-free.

We believe that the average duration of treatment should be at least one year, and we are inclined to err on the side of giving the treatment too long rather than running of the risk of a relapse by too early reëxpansion.

CHRONIC MINIMAL CASES

We have seen a few patients classed as "minimals," who have been treated over a long period of time. The area and intensity of inflammation does not increase, but as soon as any physical activity is attempted they have a relapse and return of sufficient mild symptoms to require rest treatment. We have termed these cases *chronic minimals.*

Typical of this group is

E. M., female, aged 24, a stenographer, who spent 4 years in sanatoria in Pennsylvania, was admitted to the Chicago Municipal Tuberculosis Sanitarium as a minimal case in 1933. She was treated by rest alone for 15 months. She did well except that her sputum was intermittently positive and occasionally she had some cough and expectoration. Pneumothorax was instituted on April 1, 1934. Her sputum became negative in 2 months and has remained negative to the present time. After 6 months of pneumothorax treatment, she was able to return to her former occupation.

A similar case is that of

G. M., a student, aged 18, male, who had been ill for six months at the time he was admitted to the Municipal Tuberculosis Sanitarium as a minimal case in June, 1931. He was discharged after 18 months of rest treatment as an arrested case. He spent 20 months at home on a modified rest regimen and then had an haemoptysis and reëntered the Sanitarium. On his readmission, pneumothorax was instituted immediately. After 2½ months of sanatorium treatment with pneumothorax, he was able to return home and is now back at his original occupation. When we compare 8½ months of pneumothorax treatment with 38 months of rest in this case, and five years of sanatorium-

rest regimen with six months of pneumothorax treatment in the first case, we are certainly impressed with the positive action of pneumothorax.

Four of the pneumothorax cases have shown no ill effects from childbirth. Two patients are now pregnant and are receiving pneumothorax. We believe that interruption of pregnancy in minimal cases can be avoided by giving pneumothorax during and after pregnancy.

Studying the 10 cases in which pneumothorax was recommended but not given, we find that there were 4 positive- and 6 negative-sputum cases; 3 of the 4 positive cases had been converted in 5 months, and one of the 4 is still positive. The average hospital stay for the 8 cases was 5 months. The present status of the 10 cases reveals that 3 cases (30 per cent) progressed to more advanced lesions, 6 cases (60 per cent) became arrested, and one case we were unable to locate. Of the 3 cases which progressed, 2 have already returned to the hospital for further treatment (2 cases readmitted).

A group of 65 minimal cases was treated by rest alone and was studied for comparison with the above 40 cases treated by pneumothorax. This group of 65 minimal cases was divided into positive and negative groups. There were 32 in the positive group. In 25, or 78.3 per cent, of these positive cases the sputum changed to negative in an average of 7.7 months, but 7 cases, or 21.7 per cent, did not change during or after hospital stay. The average hospital stay for 30 of these cases was 10 months (2 died). The average disability, that is, the time from the date when the patient was obliged to quit working on account of illness to the time he was discharged from the hospital, was 18 months. Of these cases, 12 were in our hospital from 1 to 4 years, and 19 were under treatment in this or other institutions for from 1 to 4 years. It should be noted here that the conversion time is much longer and the percentage of conversion is only 78 per cent. From these findings we are not surprised to note that the present status in these 32 positive cases is that only 17 cases, or 53 per cent, are well and working, while 7 cases, or 21.8 per cent, have progressed and 2 cases, or 6.2 per cent, have died. Thus a total of 28 per cent had an unfavorable outcome. Of this whole group, 6 cases, or 16.7 per cent, were not located. The important point here is that we have an unfavorable group of 28 per cent, with 2 cases which have actually died. Total disability was not estimated in this series, the figure used for comparison being the disability up to the time of discharge.

A study of the 33 negative cases reveals an average hospital stay of 6.1 months for 31 of them (2 cases died). The average disability up to the time of discharge for these 31 cases was 10.5 months. The present condition of these cases shows 15, or 45.5 per cent, favorable, and 12 cases, or 36.3 per cent, unfavorable. Of the 12 unfavorable cases, 6 still have active lesions, 4 have progressed to more advanced lesions, and two have died. There were 6 cases, or 18.6 per cent, which were not located.

The 33 minimal cases that were always negative during their stay received about the same amount of hospital treatment as the pneumothorax cases. However, when we study the present status we find that 12 cases, or 35 per cent, did not heal; moreover, 2 cases died. One of the 2 patients that died was originally diagnosed as a very early minimal case in a school survey in the State of Wisconsin, and is discussed below in the teen-age group.

Wherrett (22) reports on 291 minimal cases admitted to the Fort Q'Appelle Sanatorium, which were observed for 1 to 13 years. He found a mortality of 9.9 per cent, 23 cases that were unable to work, and 26 that still had symptoms but were working. Combining these groups, as we have done in our 65 cases, we find that he had 28 per cent of unfavorable results.

If we follow our own series further we will probably find our mortality approaching Wherrett's, but our percentage of progression is somewhat higher than Wherrett's. The fact that 80 per cent of the control cases followed in our group were X-rayed again at the time of this study may explain the higher percentage of unfavorable results. Several of our cases were supposedly well and working, but X-rays revealed an advanced lesion.

Wherrett also found a larger percentage of unfavorable results in his negative minimal cases as compared with his positive group. He suggests that this may have been due to the fact that these patients did not take their illness as seriously as the positive group.

Pope (23) has emphasized the fact that, in general, prognosis in children of the teen age, even in minimal cases, is not good. Of 34 minimal cases admitted to the Westfield Sanatorium and followed for 4 to 7 years, Pope reports a mortality of over 40 per cent. Such a mortality would indicate that the treatment of these cases needs radical revision.

The Trudeau series on the other hand, reported 77.74 per cent well,

8.4 per cent living, 7.45 per cent dead, and 7.33 per cent not located or unknown of a series of 778 cases. These results are unusually good and would justify a policy of non-interference on the basis of morbidity and mortality. The period of total disability must, however, be taken into consideration. It is our opinion that a disability of more than 6 to 12 months is unnecessary and unwarranted in minimal cases. This coincides with the opinion of Head, previously mentioned.

Our study includes 24 cases treated by interruption of the phrenic nerve. There was one case in which no paralysis of the diaphragm resulted, and this case was placed in the "rest-control group." Of these 24 cases, 17 had the phrenic nerve evulsed, and in 7 cases the nerve was crushed. All 24 cases achieved a paralysis and elevation of the diaphragm. Nineteen of the cases had a positive sputum and five were always negative. Of the 19 positive cases, 15 had positive sputum at the time of operation; 9 of these, or 60 per cent, changed to negative sputum in an average period of 6 months, and 6 cases, or 40 per cent, never changed. The average hospital stay of the 24 cases was 11.1 months. The total hospital stay was 16.4 months, and the total disability up to the time of discharge was 20.3 months.

The reason for the increased hospital stay for this group, as compared with the other two groups, is that 8 cases progressed to more advanced lesions and 4 cases remained unimproved after phrenic operations. The present status of the 24 cases thus treated shows 8, or 33.3 per cent, as progressed; 4, or 16.6 per cent, still active; one, or 4.6 per cent, died; 4, or 16.6 per cent, were arrested; and 7, or 22.9 per cent, were not located.

Of the group of 7 cases in which the phrenic nerve was crushed, 3 cases suffered a spread to a more advanced lesion, 2 cases cannot be located, one case is working, and one case is well but not working.

In the group of 17 cases in which the phrenic nerve was removed, 2 cases are working, 6 cannot be located, 8 have progressed to more advanced lesions, and 1 has died.

In making an attempt to discover why this group receiving phrenic crushing or phrenicoexairesis did not do as well, as in the groups previously described, we find, on the whole, that 10 of these 24 cases belong to the so-called "delayed" group where expectant treatment was followed. Of the 12 cases which progressed to a more advanced tuberculosis after the phrenic operation was done, 8 fall into this group of "watchful waiting" cases.

In the pneumothorax group, we reported 5 similar cases, and pointed out that these cases likewise had a much longer course of illness than the other cases. In the phrenic group, however, the operation did not check the onward progress of the disease in a satisfactory percentage of the cases.

We do not wish to evaluate definitely the effect of a phrenic operation in minimal cases from such a small series. We shall await with interest the reports from other clinics on their results from phrenic operations in minimal cases of tuberculosis.

When we compare the sputum-conversion time and the hospital stay in the 40 pneumothorax cases, the 75 rest controls (placing the 10 cases

TABLE 2

Sputum-conversion time and hospital stay

139 cases

	40 PNEUMOTHORAX CASES: 25 POSITIVE	75 REST CONTROLS: 36 POSITIVE	24 PHRENICS: 19 POSITIVE
Per cent conversion	100%*	78%	60%
	months	*months*	*months*
Conversion time	4*	7.7	6
Total hospital stay after pneumothorax or phrenic operation	6.3†	—	11.1†
Total hospital stay	8.1†	8†	16.4†
Total disability to time of discharge	11.9†	13.5†	20.3†
Total disability	14.6	—	18
	*25 cases †40 cases	†64 cases: 7 still in hospital: 4 died.	†22 cases: 1 case still in hospital: 1 died in the hospital.

in which pneumothorax was recommended but not done with the other minimal cases treated by rest alone), and the 24 "phrenics," we see that the rest controls have a lower percentage of conversions and a longer conversion time than the pneumothorax cases even though their total hospital stay averages about the same. The "phrenics" are even more unfavorable in their percentage of conversion and their conversion time. The hospital stay was much prolonged because of the relatively high percentage of cases that progressed after treatment.

When we compare the present status of these same groups (table 3) we are impressed by the fact that the mortality and morbidity of the rest controls are distinctly higher than those of the pneumothorax

group. To sum up, we find that, in this comparison, the rest controls compare unfavorably with the pneumothorax cases as to the percentage of sputum-conversion time, the percentage that is well and working, and the percentages that have progressed and the percentage that has died.

We have made an attempt in studying the 75 rest controls to pick out the cases which would later come in the unfavorable group. A comparison of symptoms, physical findings, X-ray findings, and laboratory findings has revealed no reliable criterion. The cases with positive sputum have a longer hospital stay, but the percentage of cases which progressed was higher in the negative group. This fact conforms with Wherrett's report, mentioned above.

One interesting observation, however, was made. The cases falling in the teen-age group had a rather serious outcome. Four of the nega-

TABLE 3

Present status

139 cases

	40 PNEUMOTHORAX CASES: 25 POSITIVE	75 REST CONTROLS: 36 POSITIVE	24 PHRENICS: 19 POSITIVE
Well and working	37(92.5%)*	38(50.66%)	4(16.66%)
Still active or progressed	0	20(26.66%)	12(50%)
Died	0	4(5.33%)	1(4%)
Not located	0	13(17.33%)	7(19%)

* 3 cases well, but not working: 1 diabetic, 2 unemployed.

tive-sputum control cases were of this age. Three patients are well and one died. Six of the positive-sputum control cases were of the teen age. Two have died, three have progressed to far-advanced tuberculosis and are still under treatment, leaving only one patient of this group to get well.

The case histories of two of these patients may be of interest. These cases were discovered through the surveys being made on high school students.

Case 1: In November, 1931, a 16-year-old Wisconsin high-school girl was found to have a positive intracutaneous reaction, and the X-ray showed a few findings in the left apex. The patient was without any clinical symptoms. She was permitted to finish her school year. Then she was advised to go to a sanatorium for the summer months. We placed her in a "negative" cottage, in our sanatorium on routine rest. In September, 1932, the question of re-

turning to school presented itself. We felt that she could safely attend school and discharged her as a quiescent case. In January, 1934 (16 months later), she died of far-advanced-B tuberculosis.

Case 2: In November, 1934, a 17-year-old Chicago high-school girl was found by the Chicago Tuberculosis Institute to have a positive intracutaneous test, and an X-ray made at the Municipal Tuberculosis Dispensary showed a lesion in the left apex. The patient was strongly advised to enter the sanatorium. This she refused to do because of the absence of symptoms and her desire to graduate in the spring with her classmates. The patient was permitted to attend school provided she reported every month for examination. On the March, 1935, examination she was found to have a temperature of 99°–100°, and was ordered to bed. The X-ray revealed an extensive lesion of the left side. She remained in bed for only two days, and then went back to school against advice. A positive sputum was obtained, and the patient was sent to the Cook County Tuberculosis Hospital. A pneumothorax was given on the left side and in June, 1935, she entered the Municipal Tuberculosis Sanitarium. The patient died on June 25, 1935, of a far-advanced-C tuberculosis.

There were 8 cases in the group receiving pneumothorax whose ages were between 14 and 18 years. All these cases are well, and at their usual occupation.

Pope (23) reported 22 minimal cases in the teen age, followed for 7 years with a 41 per cent mortality and 12 minimal cases of teen age admitted to the Westfield Sanatorium with a 42 per cent mortality.

We should have to conclude that any case of tuberculosis, even though in the minimal stage, carries a very definite risk, both to health and to mortality, and that every minimal case of pulmonary tuberculosis of the teen age should be given the benefit of artificial pneumothorax for a period of 12 to 18 months.

It would seem that the final outcome of these cases depends a great deal on the laws of chance, for as Allen Krause has so aptly stated, "Adult tuberculosis is the fruition of a long series of accidents." With this in view, it is logical to recommend the use of pneumothorax in any minimal case in which the diagnosis is certain, in order to cut down the incidence of these serious accidents. Pneumothorax used in this way would then become prophylactic as well as active treatment.

The rationale for the use of pneumothorax in early lesions has been greatly fortified by recent studies by Sweany (24) of 400 autopsies on patients dying of pulmonary tuberculosis. This study seems to substantiate the older theory of endogenous reinfection.

Sweany has shown that a large percentage of the cases dying of pulmonary tuberculosis have had a long series of endogenous reinfections with one partially healed lesion seeding a new one. We believe that pneumothorax is the most rational and effective means of localizing and preventing this insidious type of spread from a small beginning to the advanced stages of pulmonary tuberculosis. It is often found to be the incomplete healing of these small lesions that gives us the unfavorable results in minimal cases treated by rest alone.

SUMMARY

A study was made of the treatment and the subsequent course of all the minimal cases of pulmonary tuberculosis admitted to the Chicago Municipal Tuberculosis Sanatorium, between the years 1930 and 1935, to determine if possible the most desirable and efficient form of treatment for this type of case. The study included 139 minimal cases. Of this total, 75 cases received only the usual sanatorium routine treatment for varying periods of time, 24 received the same treatment plus a phrenic crushing or phrenicoexairesis, and 40 cases received the usual sanatorium treatment plus artificial pneumothorax. The groups were divided into those cases in which a positive sputum had been obtained, and those in which no positive sputum was ever obtained. A comparison was made of the sputum-conversion time and the percentage of conversions of the positive cases. A comparative study of the hospital stay, the total disability and the present status of these cases was made.

From the results of this study we are in complete accord with Myers and Levine (13), with the exception that we found that the "watchful waiting" policy for evidence of progression proved costly and dangerous in several cases, and even fatal in a few. Therefore, we advocate immediate induction of artificial pneumothorax in definitely diagnosed minimal cases.

We agree wholeheartedly with Alexander (2) and O'Brien (1) that minimal cases of pulmonary tuberculosis deserve serious consideration, and should be given the benefit of collapse therapy. We differ in that we favor artificial pneumothorax over the phrenic operation, because in our study the pneumothorax group did much better than did the phrenic group. The simplicity of phrenic surgery in comparison with pneumothorax is obvious. Yet the frequent contact between physician and patient, occurring during the long period of time required for pneumothorax we feel to be a distinct advantage to the patient, rather than

a disadvantage as stated by these authorities. The emphasis placed by some authorities on the risk entailed in pneumothorax treatment is in our experience unwarranted. In the series reported here and in the cases reported by Myers and Shaw, the complications so common in pneumothorax treatment of more advanced lesions were not encountered.

CONCLUSIONS

1. The operative risk in minimal cases is negligible.
2. The percentage of cases with free space is high in minimal cases.
3. The high percentage of effective collapses in minimal pneumothorax cases is a guarantee of good results.
4. Complications were so infrequent that they should not constitute a deterrent for the use of pneumothorax in early cases.
5. The conversion of sputum in positive minimal cases is prompt and certain under pneumothorax treatment.
6. The sputum-conversion time, hospital stay and total disability were definitely decreased by the use of pneumothorax.
7. Pregnancy in minimal cases is well tolerated if supported by pneumothorax.[3]
8. The conservative treatment of minimal pulmonary tuberculosis requires the early induction of artificial pneumothorax.
9. We believe that the existence of a minimal tuberculous lesion in an individual of "teen" age is an absolute indication for artificial pneumothorax without delay.

We wish to thank Dr. E. P. Troy, Superintendent of the Chicago Municipal Tuberculosis Dispensaries, for valuable coöperation in determining the present status of cases discharged from the Sanitarium. We also wish to thank the Medical Staff at the Chicago Municipal Tuberculosis Sanitarium for their assistance in compiling this report of their work in the treatment of these minimal cases.

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DANGER SIGNALS IN ARTIFICIAL-PNEUMOTHORAX THERAPY

W. M. MacKAY[1]

The practice of artificial pneumothorax in the treatment of pulmonary tuberculosis, while generally considered to be a comparatively simple procedure, is not without danger to the patient in view of the fact that accidents sometimes occur during the administration of the treatment; and, while probably unavoidable, they are nevertheless frequently serious and sometimes fatal. After the occurrence of certain disquieting episodes, one becomes impressed with the possibilities for harm and alert to the hazards associated with the operation. Of these, the most serious is air embolism or a group of symptoms considered to be the result of air embolism, although the diagnosis may not be confirmed and is hard to explain in cases occurring where air has not been introduced into the thorax.

Another complication which sometimes develops while introducing the pneumothorax needle is spontaneous pneumothorax due to rupture of the lung. This can usually be rectified if given prompt attention, but, when occurring during the induction of pneumothorax, it may not be recognized as such at the time owing to the absence of a manometer reading with the needle in the pleural cavity and the feeling consequently that a free pleural space is not present. A reading may not be obtained if the needle is plugged or if the rubber tubing does not fit snugly on the needle.

If the complications referred to can be avoided, it would obviously be wise to take the necessary precautions to eradicate them. In order to do this, certain considerations are of paramount importance, though at times accidents may occur, no matter how careful the operator may be.

Among the factors to be considered should be the circulatory system within the thorax, particularly the lesser circulation, and its arrangement in relation to the heart, lungs, and bronchi, the blood-pressure in the lesser circulation, the character and location of the lesion in the lungs,

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the extent of the pneumothorax if present, the presence of adhesions limiting the extent of the pneumothorax and their character, and the nature of the manometric response. The writer believes that if due consideration is given the foregoing, accidents may frequently be avoided. However, on the other hand, many accidents, no doubt, do not occur due to the natural arrangement of the blood-vessels in the thorax or rather the relation between the lesser circulation, the heart, and the lungs.

THORACIC PRESSURES

Under this heading is included the intrapulmonic pressure and the intrathoracic or intrapleural pressure or the pressure within the pleural cavity. The intrapulmonic pressure is the pressure in the air-passages and alveoli of the lungs and is said to be equivalent to the atmospheric pressure when the lungs are at rest. During inspiration the intrapulmonic pressure is said to fall temporarily below the atmospheric pressure to -9 or -10 mm. of water. It is said to rise during expiration to 7 or 8 mm. of water. The extent of the pressure will vary according to the type of inspiration and expiration. Howell (1) states that, when an inspiration or expiration is made with the glottis firmly closed, the pressure in the lungs rises and falls with rarefaction or compression of the contained air and that under such conditions a strong inspiration may lower the pressure by 30 to 80 mm. of mercury, while a strong expiration raises the pressure by an amount equal to 60 to 100 mm. of mercury, an example of this being the act of coughing. Riviere (2) writes that manometric fluctuations of 3 or 4 cc. of water indicate that the needle is in the lung or bronchial twig and quotes Saugman to the effect that readings as large as -6 to $+4$ may occur with the needle in the lung and that rarely, if a portion of the lung is shut off from the bronchus, a minimum pressure as low as -3 or -4 may be obtained. With reference to intrapulmonic pressure, we may cite the case of A. K. Artificial pneumothorax was being attempted in this case. On inserting the pneumothorax needle, a manometric reading in the neighborhood of -5 to $+3$ was obtained. It was felt that the needle had entered a bronchial twig, and it was withdrawn. Further attempts to find the pleural space were unsuccessful. Air introduced into the lung may enter the pulmonary circulation with disastrous results.

Intrathoracic pressures have reference to the pressure within the pleural cavity and mediastinal spaces. The intrathoracic pressure is

equal to the intrapulmonic pressure minus the elastic pull of the lung. It is always negative under normal conditions, the pressure being lower the deeper the inspiration. This again may be subject to variations depending upon the calibre of the pneumothorax needle and the rubber tubing used, the average probably being around −2 to −8.

It is therefore felt from these observations that one should not be sure of being in the pleural space unless a free oscillation of the manometer fluid on the negative side is obtained. Slight oscillation of the manometer around the atmospheric level may occur with the needle just outside the parietal pleura. Not infrequently one hears of a patient having received large amounts of air over a period of time without there later being any evidence of pneumothorax. No doubt, in some of these cases the air was introduced into the lung or bronchial passages owing to improper interpretation of the manometric readings. Again, one is reminded of certain incidents in the course of attempts at artificial pneumothorax, such as sudden coughing, blood-spitting, and tasting of the local anaesthetic by the patient, all of which, though possibly not of great import, nevertheless signify that the needle has passed through the visceral pleura into the lung or air-passages.

THE LESSER CIRCULATION

Any consideration of accidents in pneumothorax is not complete without a study of the lesser circulation which should include the pressures in the pulmonary vessels. It is felt that the greater circulation can be omitted as probably having no place in this discussion. In reviewing the anatomy of the pulmonary circulation it is necessary to consider the source, distribution, and termination of these vessels. The pulmonary artery arises from the right ventricle, divides into two branches, one to the right lung and one to the left lung, following the main bronchus to the lower extremity of the organ, other branches of these following the various branches of the bronchi. The pulmonary veins, two on each side, open into the left auricle of the heart. Their tributaries arise in capillary plexuses in the walls of the pulmonary alveoli. The smaller veins unite to form larger vessels which run along the anterior surface of the bronchial tubes and unite to form a single vessel in each lobe which passes into the root of the lung. There are, therefore, five main pulmonary veins. The veins of the upper and middle lobes of the right lung join together, and thus four terminal pulmonary veins enter the left auricle of the heart. Air entering the pulmonary arteries is blocked from entering the cerebral circulation by the lungs.

Therefore, it would probably be necessary for air to enter a pulmonary vein in order to cause an accident such as air embolism, as air entering a pulmonary vein would pass directly to the left auricle and thence might proceed straight to the cerebral circulation. It would thus appear that the main danger lies in air entering a pulmonary vein. To do this, it is not necessary for the needle to penetrate deeply into the lung in that the tributaries of the pulmonary vein arise in the walls of the pulmonary alveoli. This accident is more apt to occur where large adhesions are present as one is more likely then to penetrate the lung or tear adhesions with the needle.

INTRAVENOUS PRESSURES AND AIR EMBOLISM

The most dreaded complication in pneumothorax therapy and fortunately the least common is air embolism. In order to explain the occurrence of this accident, it is necessary to recall the distribution of the lesser circulation and to note the blood-pressure in it. Howell (3) states that the blood pressure in the pulmonary arteries is low, namely, in the cat, 10 to 33 mm. mercury; in the dog, 7.5 to 24.7 mm. mercury; and in the rabbit, 6 to 35 mm. mercury; but that it is higher than in the capillaries and higher in the capillaries than in the pulmonary veins. Air entering the pulmonary arteries is carried to the lungs, and hence blocked from entering the brain, and so air entering the pulmonary arteries probably would not be a cause of air embolism. At this point we wish to mention the case of C. D., one of unilateral pneumothorax, there being about 50 per cent collapse of the right lung. In the uncollapsed portion of the lung were several moderate-sized cavities. There were many large adhesions extending between the lung and chest-wall. There was some fluid in the pleural cavity. A pneumothorax refill was about to be given. The needle was inserted through the pleura and the manometric reading taken. There was a gradual rise of the water on the positive side of the manometer but no oscillation. It was felt that the needle had entered a branch of the pulmonary artery and it was withdrawn. A small amount of blood was then expelled from the pneumothorax needle and the rubber tubing. Another location was chosen for insertion of the needle, and the refill was given without mishap.

It has been generally noted that the venous blood-pressure is negative and, with reference to the chest, this has been proved by experiments on the central veins of the thorax. Tigerstedt (4) states that the pressure in the superior vena cava of the dog close to the right auricle is -3 mm. mercury and in the distal portion of the same vein, -1.4 mm. mercury.

Apparently little or no work has been done on the pulmonary veins to estimate the pressure in these veins, but this is assumed to be negative. Howell (5) states that in the closed chest pressure in these veins probably differs only slightly from that of the left auricle, which is −2 to −50 mm. water on inspiration and +6 to +38 mm. water on expiration. Wiggers (6) states that the pulmonary venous pressure within the closed thorax probably approximates that found in the left auricle, which is zero, or less during inspiration, and becomes only slightly positive during expiration. He also states that these pressure changes are not capable of being directly studied without great chance of error. Air entering a pulmonary vein would appear to be the main source of air embolism owing to the course of the blood-stream in these veins which flows to the left auricle and thence may proceed to the brain. This complication was demonstrated by McCurdy (7) who cites the case of a patient who was being given a pneumothorax refill in which air embolism occurred. The manometer had registered a marked negative pressure, following which 200 cc. of air was given. The diagnosis was proved at autopsy, the needle hole in the wall of the pulmonary vein being demonstrated. Air was also demonstrated in the right heart, the vessels on the convex surface of the cerebrum, and in the inferior vena cava.

However, cases are on record in which a group of symptoms was exhibited suggestive of air embolism where no air was given. This has been explained in various ways, such as suction of air from the rubber tubing connected with the pneumothorax needle. The writer feels that in these cases, while embolism is probably the cause of the symptoms, it may be due to dislodgement of a blood-clot or caseous material, which is carried by the blood-stream to the brain. In this connection we cite the case of L. M., one of bilateral pneumothorax in which refills had been given for many months, resulting in a selective collapse bilaterally. Dense adhesions had formed in the right pleural cavity toward the base. A refill was about to be given on the right, the manometer valve having been opened to obtain the reading, when the patient developed a syndrome consisting of a sharp exclamation as of pain, stertorous breathing, cyanosis, weak pulse, dilated pupils, involuntary urination, and coma. The patient regained consciousness in approximately two hours, when he complained of severe headache, nausea, vomiting, and complete loss of vision. Vision gradually returned, so that the following day it appeared normal, although the patient felt for some time that his eye-

sight was not so good as formerly. Pneumothorax was discontinued and the patient ran a gradual downhill course. Approximately three months following this episode, the man developed meningeal symptoms and died. It is not known whether this accident had any bearing on the terminal condition of the patient or not. In all probability air embolism will rarely occur if a free oscillation of the water in the manometer on the negative side is obtained.

SPONTANEOUS PNEUMOTHORAX

This complication occurs not infrequently, and probably much more often during pneumothorax refills than is generally recognized. This is amply demonstrated by fluoroscopy shortly following the pneumothorax refill when the extent of the pneumothorax is found to be much greater than can be accounted for by the amount of air given. In the majority of such cases, it is the result of a small puncture of the lung and few or no symptoms are manifest. On the other hand, symptoms may develop while the patient is on the table and pneumothorax is being attempted, probably the result of puncture of a caseous area and resulting in severe and typical symptoms of spontaneous pneumothorax. This accident is probably rare. As an example of this, we cite the case of E. M. This is the case of a patient with a nervous and irritable temperament. Pneumothorax had been advised for a lesion in the left lung. The patient was very apprehensive upon getting on the operating table. He complained of severe pain while the needle was being inserted. The pleura appeared adherent, as a manometric reading was not obtained and it was felt that the attempt at pneumothorax was unsuccessful. The patient was still uncomfortable on leaving the operating room but stated that he felt much better. A short time later he began to complain of dyspnoea and pain in the left side. Fluoroscopic examination of the chest showed the presence of considerable pneumothorax. The pneumothorax needle was inserted in the pleural cavity and a negative pressure noted. A small amount of air was removed with relief, but the symptoms recurred during the day and were relieved by opiates. Two weeks later a refill was given; and the pneumothorax is still being maintained, the patient having been discharged from the sanatorium and returned to his home. The incidence of spontaneous pneumothorax is probably directly proportional to the severity and type of the pulmonary lesion, independent of the treatment given. It occurs not infrequently in the presence of caseous disease, with or

without cavitation. It may occur in the presence of artificial pneumothorax where the same conditions exist if the lesion or cavity remains uncollapsed owing to the presence of adhesions or other causes.

CONCLUSIONS

1. During the induction of artificial pneumothorax, certain abnormal features will at times be noted and should be recognized as danger signals.

2. Slight manometric fluctuations may be noted with the needle in the neighborhood of the parietal pleura and are not an indication that the needle is in the pleural space.

3. When the needle is in the lung or air-passages, a free manometric reading ranging from negative to positive may be obtained. The reading may indicate the normal intrapulmonic pressure for the individual and should not be confused with the intrapleural pressure.

4. The pressure in the pulmonary veins is said to be negative and may be confused with the intrapleural pressures, but this rarely happens.

5. Coughing, blood-spitting, and tasting of the local anaesthetic by the patient not infrequently occur during induction of pneumothorax and indicate that the pneumothorax needle has passed through the visceral pleura into the lung.

6. Adhesions may be a source of danger during refills in that if torn air may enter the pulmonary veins.

7. Sudden severe pain occurring during the attempt to induce pneumothorax may indicate that a spontaneous pneumothorax has developed. The absence of a manometric reading is no criterion that a spontaneous pneumothorax has not developed.

8. If free oscillations of the manometer fluid on the negative side are obtained, accidents will be rare.

9. Accidents at times are unavoidable, even when the most meticulous care is taken to avoid them.

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THE AMERICAN REVIEW OF TUBERCULOSIS

JOURNAL OF THE NATIONAL TUBERCULOSIS ASSOCIATION

ABSTRACTS OF TUBERCULOSIS

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VOLUME XXXIV

JULY-DECEMBER, 1936

PUBLISHED MONTHLY

AT MT. ROYAL AND GUILFORD AVENUES, BALTIMORE, MD.
BY THE NATIONAL TUBERCULOSIS ASSOCIATION

THE

AMERICAN REVIEW OF TUBERCULOSIS
ABSTRACTS OF TUBERCULOSIS

VOLUME XXXIV SEPTEMBER, 1936 ABST. No. 1

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Psychoneurotics and Functional Disorders.—One is puzzled trying to understand the troubles of a large group of patients seen commonly in certain large clinics. They usually expect some sort of surgical miracle, while the average doctor is apt to dismiss them as "merely neurotic." Among their most trying symptoms are a feeling of fatigue, discouragement, inadequacy and discomfort in the head. Several practical questions ought to be asked them, but they seldom are asked. If they have not worked for some time, or fear to do so, or cannot face people, one gets a clue to investigate the nervous system rather than some other organ, as the stomach. Also they usually sleep badly. They lack interest in life, and are demoralized. Frequently they have had insane, psychopathic or epileptic relatives. Their heredity or germ-plasm is defective, and the family or relatives will have noted some changed behavior even though in your presence they do not act amiss. The modern physician is badly trained in handling nervous and psychopathic patients. Even if mental behavior is regarded as abnormal, the doctor's mind reverts to foci of infection, the colon, the glands of internal secretion, and what not. A lot of these poor people are futilely operated on repeatedly and always become worse. Do not tinker with such details as teeth, tonsils or hernias in those patients. A prolonged rest-cure should be advised. Not only does this train of symptoms occur in the inadequately equipped under normal conditions, but in the mentally and physically capable under circumstances of strain. What many physicians need is to go through a nervous breakdown themselves. Also, one should never advise operation on a purely X-ray diagnosis. And the term "colitis" should be abandoned unless there is demonstrable ulceration or inflammation. A spastic colon is not a disease and the term is misleading thus applied. Likewise the diagnosis of visceral ptosis is to be avoided and of retroverted uterus. If there is marital discord its treatment will not help. New fears should not be implanted. Physicians too often fail to recognize frank insanity, and surgeons have been shot by such patients after operating on them. Probably more psychopathic persons consult gastroenterologists than any other kind of specialist. Psychic and behavior changes following severe incapacitating illness should also be recognized. The existence of insane or abnormal relatives should always be investigated. Too often people know little about their relatives, especially those dead or divorced. Besides actual insanity, there are equivalents such as cranks, periodic drinkers, mystics, religious fanatics and violent reformers, criminals and blatant politicians. While many are both mental and physical weaklings, others are well built, able and brilliant. Nevertheless, they are inadequate to the strain of life and menaces to civilization. Modern sanitation now prolongs their lives and they are frequently both voters and government wards. Mostly, they are a financial problem because they have little money or resources. Many are lovable characters but they cannot be remade. They go to pieces with excitement or slight change in routine. What financial